IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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SHIRE ORPHAN THERAPIES LLC and SANOFI-AVENTIS DEUTSCHLAND GMBH,	)	Civil Action
Plaintiffs,	)	
v.	)	
FRESENIUS KABI USA, LLC,	)	
Defendant.	)	No. 15-1102-GMS

- - -

Wilmington, Delaware
Monday, January 29, 2018
9:00 a.m.
Trial Day 1

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Senior Judge, U.S.D.C., District of Delaware

APPEARANCES:

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09:05:01

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09:05:01 **THE COURT: Good morning. Please, take your**
09:05:04 **seats.**
09:05:04 **(Counsel respond "Good morning.")**
09:05:06 **THE COURT: I thought this was a two-party case.**
09:05:11 **No?**
09:05:14 **Mr. Blumenfeld, would you start.**
09:05:18 **MR. BLUMENFELD: Thank you, Your Honor.**
09:05:19 **Jack Blumenfeld from Morris Nichols for the**
09:05:21 **plaintiffs Shire and Sanofi. I am not going to try to**
09:05:24 **introduce all the people in the courtroom.**
09:05:27 **Ed Haug and Sandra Kuzmich will be taking the**
09:05:32 **lead for the plaintiffs.**
09:05:35 **And we have a number of people here from Shire,**
09:05:39 **in-house counsel, Jason Baranski, Jim Harrington, and Kevin**
09:05:44 **McGuff.**
09:05:44 **Thank you, Your Honor.**
09:05:50 **THE COURT: Ms. Keller.**
09:05:51 **MS. KELLER: Good morning, Your Honor. Karen**
09:05:53 **Keller from Shaw Keller on behalf of Fresenius Kabi. With**
09:05:56 **me today on behalf of Fresenius is Daryl Wiesen, Bill James,**
09:06:06 **Coy Stull, and Sam Sherry of Goodwin Procter, and in the**
09:06:09 **back is Ali Ahmed from Fresenius.**
09:06:14 **(Counsel respond "Good morning.")**
09:06:14 **THE COURT: Are we ready?**
09:06:17 **MR. WIESEN: We are, Your Honor. We will**

09:06:19 distribute some copies of some slides, if you would like
09:06:26 them.
09:06:59 THE COURT: Good morning.
09:07:00 MR. WIESEN: Good morning, Your Honor.
09:07:03 The question for this trial is whether Claim 14
09:07:07 of the '333 patent owned by Sandoz and licensed to Shire is
09:07:12 valid and enforceable.
09:07:13 The only asserted claim of the '333 patent at
09:07:23 issue is Claim 14. It claims a single compound, the
09:07:28 ten-amino-acid peptide icatibant.
09:07:32 As the evidence will show here, Shire got
09:07:35 another patent that claims the same discovery as the '333
09:07:39 patent, the same structural change from the prior art that's
09:07:42 contained in this patent is contained in the '7,803 patent
09:07:53 that Shire also obtained.
09:07:57 That patent already expired. Shire is not
09:08:01 entitled to the second patent but claims an obvious variant
09:08:06 of the first under obviousness-type double patenting. So
09:08:12 Claim 14 is invalid.
09:08:14 Actually, icatibant was identified before the
09:08:17 compounds in the '7,803 patent, and in fact the application
09:08:20 that resulted in the '333 patent was filed first.
09:08:23 Why did the '7,803 patent issue before the '333
09:08:27 patent? The answer is the second defense in the case, that
09:08:31 is because Shire or Shire's predecessor, Hoescht, to develop

09:08:36 the compound, spent more than four years simply stalling
09:08:41 prosecution, doing nothing but getting a rejection, filing a
09:08:48 continuation, getting the same rejection, filing another
09:08:49 continuation, getting another rejection, filing another
09:08:53 continuation, for four years.
09:08:54 That delay in the issuance of the '333 patent is
09:08:57 why the '7,803 is a reference for obviousness-type double
09:09:01 patenting and renders the '333 patent unenforceable for
09:09:05 prosecution laches.
09:09:09 Let me turn to what the evidence will show.
09:09:12 The '333 patent in suit discloses and claims a
09:09:16 genus of what are called bradykinin antagonists.
09:09:25 These compounds prevent bradykinin, a naturally
09:09:31 occurring peptide in the human body, from having its natural
09:09:34 effect. The compounds at issue in this case are also
09:09:37 peptides. They are chains of amino acids that are strung
09:09:40 together like beads on a chain.
09:09:42 By convention people of ordinary skill in the
09:09:46 art abbreviate them with three or four letters, and that is
09:09:49 how we will do it throughout the case.
09:09:50 Claim 14 of the patent on the next slide
09:09:55 describes the ten amino acids in icatibant. There is an H
09:10:01 on one end and an OH on the other end to tell us what is at
09:10:02 one end, what is the N-terminus, and the C-terminus, H is
the N and OH is the C, and then there is the ten amino acids

in the middle, D-Arg, Arg, Pro, Hyp, Gly, Thia, Ser, D-Tic, Oic, and Arg. And we will have experts here to explain all of this.

The first U.S. application in the family was filed on June 30, 1989. According to Shire, the '333 patent will not expire until July 15, 2019. That is 30 years later from the U.S. application.

It is the propriety of that ultra-long patent right that will be the main issue in this trial.

Now, to go back earlier than 1989, to the mid-80s, a number of researchers and companies were focused on research concerning bradykinin. The naturally occurring bradykinin peptide is made up of 9 amino acids. That was known by the mid-eighties and it was specifically known what order they were in. We put it up here on the slide.

When chemists and experts spoke about bradykinin or any peptide in particular, they would number the positions so you could just talk about them commonly. So you have got 1 through 9 as the amino acids in bradykinin.

Now, for the people who were looking for these, they were looking for bradykinin antagonists. What does that mean? What is an antagonist? An antagonist is something that blocks the activity of the natural compound. An analogy you will hear about is a lock and key. Bradykinin receptors are the lock, bradykinin is the key.

09:11:38 It fits in the lock and turns it. It activates a bradykinin
09:11:41 receptor.
09:11:41 A bradykinin receptor is the other key on your
09:11:46 key chain. You put in your front door, it doesn't turn. It
09:11:50 won't activate the lock. Won't open it up. But it prevents
you from putting the locking key in. It blocks the
09:11:55 activity. That is what an antagonist is and what people
09:11:58 were looking for. They were trying to block the activity of
the bradykinin.
09:12:03 Why do you want to do that? Bradykinin is
09:12:05 naturally produced in the human body, it seems like a good
09:12:09 thing, not a bad thing. The problem is people theorized
09:12:14 that diseases were caused by an excess of bradykinin.
09:12:14 So for people with those diseases you want an
09:12:15 antagonist to tamp down the amount of bradykinin to produce
09:12:20 to treat the disease.
09:12:21 To be sure, in 1989 those were just theories.
09:12:24 There were no diseases that were treated with a bradykinin
09:12:28 antagonist. But people were looking for bradykinin
09:12:31 antagonists on that theory.
09:12:33 The first thing you need to do that though is to
09:12:36 have a bradykinin antagonist, something that would block it.
09:12:42 Everybody in the case will agree that by 1989, the priority
09:12:45 date here, bradykinin antagonists had been found. Two
09:12:51 professors at the University of Colorado, John Stewart and

09:13:04 **Ray Vavrek, had discovered bradykinin antagonists. They**
09:13:08 **were leading that search and they published about them. You**
09:13:11 **will hear about this from Dr. Bavchovchin.**
09:13:14 **If we go to the next slide, he is a professor at**
09:13:18 **Tufts University. He has been working with peptides for his**
09:13:23 **entire career, including at the time.**
09:13:24 **He will explain the work that was going on and**
09:13:27 **the background on peptide chemistry and how people were**
09:13:29 **looking for bradykinin antagonists.**
09:13:32 **How did Dr. Stewart and Dr. Vavrek look for**
09:13:37 **bradykinin antagonists? They started with bradykinin. They**
09:13:39 **knew that fits into the receptor. And they started making**
09:13:43 **changes. They started changing some of the amino acids**
09:13:46 **around, to see what happens, see what they could develop.**
09:13:50 **At that point, these beads on the chain, these**
09:13:52 **peptides or amino acids were pretty easy to make. By the**
09:13:57 **late eighties, it was an automated process. You basically**
09:13:57 **typed in the sequence you wanted and the automated equipment**
09:14:04 **spit out those peptides. It was made by a process called**
09:14:06 **solid phase synthesis, which you are going to hear about in**
this case.
09:13:53 **Now, Dr. Stewart started with the nine amino**
09:13:56 **sequence in bradykinin and changed some of the amino acids**
09:14:00 **to other amino acids. We've put up here one of the Stewart**
09:14:05 **bradykinin antagonists that he developed and that was**

09:14:08 published in the prior art. Perhaps most importantly, Dr.
09:14:11 Stewart discovered that making the changes at the seven
09:14:13 position, which we've put in a circle here, was critical to
09:14:19 creating an antagonist. If you made particular changes in a
09:14:22 particular, what's called a D-aromatic amino acid, again,
09:14:26 Dr. Bachovchin will explain that, in the seven position, you
09:14:30 flip the activity. It went from being an agonist to an
09:14:34 antagonist, and that was an important discovery. That was
09:14:36 the first time anybody made a bradykinin antagonist. Those
09:14:43 were disclosed in the prior art.
09:14:45 Now, Dr. Bachovchin is going to explain other
09:14:47 changes that Dr. Stewart and Dr. Vavrek published and
09:14:52 explained, and we'll focus here just briefly on two of them.
09:14:55 First, at what's now labeled the zero position. An extra
09:14:59 amino acid got added in at the end terminus on the left end.
09:15:05 We call it the zero position, or people of ordinary skill in
09:15:08 the art call it the zero position because we want to keep
09:15:10 the one through nine the same as bradykinin so it matches up
09:15:13 when we talk about numbers, so we add zero and we could
09:15:15 see a negative one and a negative two off the left end so
09:15:19 that we keep the one through nine matching up with
09:15:21 bradykinin.
09:15:22 And what Dr. Stewart published is if you put a
09:15:25 D-Arginine amino acid at the N-terminus at the left-hand
09:15:30 side, that also improves the activity and helps the amino

09:15:33 acids not break down as quickly in the body.

09:15:36 The other change you'll hear about from Dr.
09:15:40 Bachovchin is at the eight position. The published research
09:15:42 included a structure-activity relationship of the work that
09:15:47 had been done and Dr. Vavrek and Stewart published that you
09:15:53 could make changes at the eight position. Here we've put in
09:15:56 the rest of the numbers to their patent. So you see that
09:15:59 zero through nine and you see a long list of possible
09:16:01 substitutions at the eight position. You'll see some other
09:16:04 prior art references that talk about the eight position and
09:16:07 include a proline there, and Dr. Bachovchin will explain a
09:16:11 POSA would know that bradykinin antagonists can have
09:16:15 different amino acids in the eight position and when the
09:16:17 POSA gets to considering the validity of claim 14, they know
09:16:21 all of this. This is all in the prior art, and a POSA
09:16:25 understands what a bradykinin antagonist looks like when get
09:16:30 to the question of obviousness-type double patenting.

09:16:33 So let's look at the research that Hoechst did.
09:16:36 At least that's how I pronounce it. We'll find out from Mr.
09:16:40 Haug the right way to pronounce it.

09:16:42 When the inventors did this project in 1989, a
09:16:47 POSA knew about bradykinin and they knew about the ten amino
09:16:51 acids of the Stewart bradykinin antagonist. You'll hear
09:16:54 testimony about this compound, the Stewart bradykinin
09:16:57 antagonist. It has got numbers because it never became a

09:17:00 commercial product. It's called either NPC 349 or B3824.
09:17:07 That's the same thing. People just called it different
09:17:09 numbers in the art for various reasons that you hear about.
09:17:13 And this was recognized as a pretty standard compound in the
09:17:16 art.

09:17:18 So what did the Hoechst researchers do? They
09:17:20 came up with icatibant, which was previously known, you'll
09:17:24 see, and its number was HOE 140. You'll see some papers
09:17:27 about that. And it has the following structure. This is
09:17:33 the '333 patent, claim 14. They changed two amino acids at
09:17:38 the seven and eight position and with those two changes to
09:17:40 the Stewart compound, they got icatibant. Shire's argument
09:17:45 throughout the case and during prosecution was making these
09:17:48 two changes is not obvious. This is two changes out of ten.
09:17:51 That's inventive.

09:17:53 So what's our argument? Why is that invalid?
09:17:56 It looks like they've changed this compound around. The
09:17:59 problem, Your Honor, is, the '333 patent is not the first
09:18:03 patent they got with D-Tic in seven and Oic in eight.
09:18:09 Those critical changes, they got a prior patent that makes
09:18:12 exactly those changes. You saw this in the motion to amend
09:18:15 that we talked about. It's the '7,803 patent, and Claim 1
09:18:18 of the '7,803 patent includes a group of compounds, but
09:18:23 focuses on D-Tic at the seven position and Oic at the eight
09:18:29 position. That's what they said their invention was and

09:18:31 they already got a patent. They claimed that and now it has
09:18:38 expired.
09:18:39 That patent, by the way, Your Honor, was not
09:18:41 disclosed during prosecution of the '333 patent. The Patent
09:18:44 Office has never looked at the argument and the evidence
09:18:46 that we're presenting here.
09:18:48 Now, because of the long time it took to get the
09:18:51 '333 patent because of the stalling tactics that we'll talk
09:18:54 about in a little while, there's no question that the '7,803
09:18:57 patent qualifies as a reference for obviousness-type double
09:19:00 patenting.
09:19:01 We put up the cover pages of the two patents
09:19:05 here. The '7,803 patent issued first. It's already
09:19:10 expired. The assignees the same, both of them Hoechst, and
we've highlighted the numerous inventors that overlap as
09:19:19 well. With that, it clearly qualifies as an
09:19:22 obviousness-type double patenting reference and renders the
09:19:24 '333 patent invalid.
09:19:26 Let's look at the Claim 1 of the '7,803 patent,
09:19:32 because in an obviousness-type double patenting analysis, we
09:19:36 compare the claims to see whether they're obvious variants
09:19:39 of each other. Claim 1 of the '7,803 patent is
09:19:42 unfortunately not as straightforward as Claim 14, as the
09:19:47 compound claim in the '333 patent. It looks like it has got
09:19:50 a long list, but we can break down what they've claimed

09:19:53 here. It's basically a long list of compounds. It's a
09:19:56 genus, but it's a genus where a person of ordinary skill in
09:20:00 the art could read this and could literally write down every
09:20:03 single claim, every single compound that's covered. And you
09:20:07 know for obviousness-type double patenting, we don't have to
09:20:11 prove a so-called lead compound. Any compound that's
09:20:13 claimed, we can start with, and we'll start mainly with one
09:20:16 of the claims that a person of ordinary skill in the art
09:20:18 would see in Claim 1.
09:20:21 So if we break down Claim 1 and we start with B
09:20:26 through I of the locations, that's pretty straightforward,
09:20:29 because almost all of them, there's no options. The only
09:20:32 option is at the G position, and that's three choices, one
09:20:37 of which is Oic. And you'll hear Oic as an amino acid a
09:20:41 lot. We've numbered it here as in the bradykinin
09:20:44 antagonist, and you'll see, this matches up with icatibant
09:20:49 except its missing that D-Arg at the zero position, and
09:20:53 that's clearly undisputedly part of Claim 1.
09:20:55 If we add the A in, A is four or five options, D
09:21:02 or L-Arg, or D or L-Lys or the bond, and a bond just means
09:21:05 it's nothing. And so if we go A through I, and I is just OH
09:21:10 at the end telling us that's the C terminus -- if we go A
09:21:14 through I, it's icatibant. That's what's disclosed. That's
09:21:21 what's claimed. No question about it.
09:21:22 And while the person of ordinary skill in the

09:21:23 art, if they were comparing with the prior art, would see
09:21:26 that seven and eight is a little bit different than Stewart.
09:21:29 Right. There's no prior art with a D-Tic in the seven
09:21:31 position and an Oic in the eight position. It sure looks
09:21:34 like the Stewart compounds and although it's different amino
09:21:38 acids, it's consistent with Stewart's teachings. It's a
09:21:41 D-aromatic amino acid in the seven position. It's an Oic in
09:21:45 the eight position, which is similar to proline and other
09:21:47 things that Stewart taught, and so a person of ordinary
09:21:51 skill in the art would see this claim and would think, that
09:21:54 looks like a bradykinin antagonist.

09:21:57 All right. But that's not all that's claimed
09:21:59 and I'm sure we're going to hear that from Shire. Right.
09:22:02 What's on then the left end? We have to add the Z and the P
09:22:08 groups that are at the beginning of the claim.

09:22:13 The list, the first thing listed in the Z group
09:22:16 is what's called an Fmoc, and the first thing listed in the
09:22:20 P group is a direct linkage. Direct linkage is like a bond.
09:22:24 There's nothing there. You just directly link from Z to A.

09:22:28 And so the POSA would see as we've drawn out on
09:22:32 slide 1-20 that specifically claimed is what we call Fmoc
09:22:37 icatibant, Fmoc at the beginning and then the icatibant
09:22:41 sequence. Now, a POSA is going to know a lot about this
09:22:44 Fmoc group and actually all the groups that are in Z.
09:22:48 They're important in peptide chemistry but not because

09:22:51 they're amino acids. Fmoc is actually not an amino acid.
09:22:54 It's a different chemical group. But it's important because
09:22:59 it's known not as what's in final product, it's known as a
09:23:03 protecting group, as something you use when you make a
09:23:06 compound. And it's known, it's very easily removed.
09:23:11 So what one sees, we've put up here just the
09:23:17 Bodanszky reference. It's a well-known peptide chemistry
09:23:19 book and it talks about what one does with Fmoc is take it
09:23:23 off. That's what it's born for, that's what it's it exists
09:23:26 for, that's what it was created for in synthetic chemistry,
09:23:31 is to take it off the group and see what's being made. And
09:23:34 when a POSA sees that Fmoc, they think, hmm, this looks like
09:23:38 an intermediate. It looks like the compound is not there.
09:23:41 Not done yet and let's see what happens. Let me give you a
09:23:44 little bit.
09:23:45 You'll hear from Dr. Bachovchin about synthetic
09:23:50 solid-phase synthesis, how these compounds are made, and I
09:23:53 talked a little bit about the fact that what you do is you
09:23:55 build the chain up amino acid by amino acid, but you don't
09:23:59 actually add an amino acid. You add what's called a
09:24:02 protected amino acid, which puts one group on the amino end
09:24:05 and it does that so chemically, that can't react, because
09:24:09 you want to make sure you put the amino acids in order. If
09:24:13 you don't put that protecting group, which we've illustrated
09:24:17 with the little orange cap, then this is what you get.

09:24:19 Instead of going one amino acid at a time, they'd all
09:24:22 connect up together.
09:24:23 So a protecting group is there to stop that from
09:24:27 happening and generally what happens is you put on an amino
09:24:30 acid with a protecting group. Then you take off the
09:24:32 protecting group. Then you put on another amino acid which
09:24:35 attaches with its protecting group. Then you take off the
09:24:38 protecting group and you build the chain that way and at the
09:24:40 end, you take it off and you take off that last protecting
09:24:43 group to get your compound.
09:24:45 Now, I don't think there's going to be a dispute
09:24:49 in the case that Fmoc was well-known as a protecting group.
09:24:55 In fact, we asked one of the inventors, Dr. Knolle, and he's
09:24:59 going to appear by deposition because I understand he has
09:25:01 taken ill. But we asked him: What about the Fmoc? What do
09:25:07 you do? He said, in that answer, when you say at the end of
09:25:10 the synthesis you mean the N-terminal amino protecting
09:25:13 group, you meant you remove the Fmoc, right? And his answer
09:25:16 was, always, yes.
09:25:17 There's not really a dispute that the Fmoc gets
09:25:20 removed and it's easily removed. As a matter of chemistry,
09:25:24 Fmoc was very popular because it was easy to take off
09:25:27 without otherwise taking off the chain of amino acids
09:25:31 because that's what we want to do. Right. You don't want
09:25:33 to take off that protecting group and also break up the

chain that you just may have spent all that time building.

So when a POSA sees Fmoc-icatibant, they think, what's that Fmoc doing there? That should come off. This looks like an intermediate. And they recognize that if you take the Fmoc off, it looks a lot like a Stewart bradykinin antagonist. So the first thing a POSA would do when they see the compound of Claim 1 of the '7,803 patent is remove the Fmoc, and when they do, they get icatibant, and that's the obviousness-type double patenting argument. That's the reason that the patent is invalid.

Now, Your Honor is going to be the first one to look at this issue because it didn't come up during prosecution. Even though the same company owned the applications and the same inventors were involved, and the same law firm was prosecuting the patents at the same time, the application that resulted in the '7,803 patent was never presented to the examiner who was analyzing the '333 patent.

Now, the plaintiffs have raised a claim construction argument. We wrote some letters and had a short call about it, and I want to spend a minute trying to explain why I think that has come up, because initially we told you there were no claim constructions in the case, and, of course, if you look at the claims, that makes sense. They're claims to compounds.

09:26:55 Nothing needs to be construed in this. There's
09:26:57 no ambiguity. We almost never have a claim construction
09:27:00 hearing when there's a compound claim because we can all
09:27:02 read this and know what's covered.
09:27:05 Shire has proposed reading in particular
09:27:07 activity to these claims that it has to be known as a
09:27:11 bradykinin antagonist. Why? We think the answer -- we
09:27:15 don't know, it came up late in the expect reports. We think
09:27:18 the reason for that is because they want the claims to be
09:27:20 construed to be final compound so it won't be an
09:27:24 intermediate so the POSA won't take the Fmoc off, because if
09:27:28 the '7,803 patent they think claims a final compound, it
09:27:32 wouldn't be obvious to make the change and take the Fmoc
09:27:34 off.
09:27:35 We think that's wrong for two reasons, Your
09:27:37 Honor. We think it's wrong because it's wrong as a matter
09:27:40 of claim construction. There's no activity required here.
09:27:42 If you have the compound, you infringe no matter what it's
09:27:46 used for, no matter if it's a bradykinin antagonist or not.
09:27:49 But we also think even if it's the case that the claims
09:27:52 require activity, it's still obvious. Even if you might
09:27:55 think, oh, that compound in the '7,803 patent is an active
09:27:59 compound itself, a POSA would also look at it and think,
09:28:04 but, boy, I also ought to check what the more standard ten
09:28:08 amino acid Stewart-like bradykinin antagonist is. I think

09:28:12 it's going to work. Maybe it won't work better. Maybe it
09:28:15 will. But they're certainly going to take the Fmoc off and
09:28:19 find out. And because of that, they're motivated to make
09:28:22 the change, and they'll think that it's going to be a
09:28:24 bradykinin antagonist, and that's enough to make it obvious.
09:28:27 Now, finally, Shire is also going to spend some
09:28:32 time talking about secondary considerations, and we talked
09:28:35 about that a little bit at the final pretrial conference.
09:28:38 The problem is that Shire hasn't established any nexus for
09:28:41 obviousness-type double patenting. Why? Why is it
09:28:45 different than a standard obviousness case?
09:28:48 If we think about secondary considerations or
09:28:50 objective indicia, as they're also obviously called, the
09:28:54 idea is, people in the real world, if there was a motivation
09:28:59 either scientifically or financially to combine two things
09:29:03 together, people would do it. That just logically makes
09:29:08 sense, and the fact that people didn't do it would mean that
09:29:12 it must not be obvious. But an assumption in that logic is
09:29:16 that the people in the real world have the necessary
09:29:19 information. Most of the time that's true. Right. It's in
09:29:22 the prior art. That's why we do the analysis. And so they
09:29:25 could look at the two papers and combine them if they want
09:29:28 to.
09:29:28 But obviousness-type double patenting is a
09:29:30 little bit different. The '7,803 patent is not actually in

09:29:34 the prior art. We act like the claim is prior art for the
09:29:38 legal analysis, but nobody in the real world actually saw
09:29:43 this patent back in 1989.
09:29:46 So without some explanation for how long-felt
09:29:52 need or commercial success demonstrates nonobviousness,
09:29:53 without some nexus evidence, the argument falls apart in
09:29:57 obviousness-type double patenting. And Shire has no nexus
09:30:01 evidence. They have not spent any time or explained why it
09:30:04 is that a person of ordinary skill in the art would or could
09:30:07 have made this combination in the real world, because
09:30:10 obviousness-type double patenting is not based on what was
09:30:14 actually available in the real world. The way the argument
09:30:17 is set up is to prevent them from extending the patent life,
09:30:21 but it's not something that was actually known.
09:30:24 Now, if we turn briefly to Firazyr and Shire's
09:30:29 product, it treats a disease that I'm sure you're going to
09:30:33 hear about called hereditary angioedema. No dispute it's a
09:30:37 serious disease where a genetic defect causes uncontrolled
09:30:39 swelling. If undiagnosed, it can be life-threatening.
09:30:43 Luckily today, there are a number of approved treatments.
09:30:46 We've got some up here on the screen.
09:30:51 Firazyr was icatibant. And Firazyr was not even
09:30:53 the first treatment discovered. It wasn't the first
09:30:55 approved worldwide. It wasn't the first approved in the
09:30:58 U.S. And while Shire, as I'm sure we'll hear, makes a lot

09:31:02 of money from selling the drug, even though, Your Honor,
09:31:05 you'll also hear, there are fewer than 5,000 people treated
09:31:08 in the United States with this disease. It's sort of an
09:31:11 ultra orphan. It's a very small population. They presented
09:31:15 no evidence, Shire, that any difference between icatibant
09:31:19 and the compound in the '7,803 patent is what leads to these
09:31:23 sales and the success. And Dr. Bachovchin will explain why
09:31:28 some of the prior art attributes are actually what drives
09:31:31 it. That, and we'll hear although it's supposedly a better
09:31:35 product, they price it below its competition. We think that
09:31:37 explains the sales, not the patent.
09:31:39 In the end, Your Honor, when the '7,803 patent
09:31:42 expired, the defendants should have been able to use all of
09:31:46 those compounds and their obvious variants. And since
09:31:51 icatibant is an obvious variant of that previous patent,
09:31:54 claim 14 of the '333 patent is invalid for obviousness-type
09:31:59 double patenting.
09:32:00 Let me turn more briefly, Your Honor, to the
09:32:02 second argument we'll talk about, prosecution laches. The
09:32:05 applicant spent years stalling prosecution of the '333
09:32:08 patent with no explanation. Because of that delay, the
09:32:12 '7,803 patent actually issued before the '333 patent and
09:32:16 made it a double patenting reference. But the '333 patent
09:32:22 is also invalid or unenforceable because of that delay,
09:32:25 because of prosecution laches.

09:32:41 We have put up here, this is the list of the
09:32:44 Stewart bradykinins, and all the related applications, Your
09:32:47 Honor. We have circled in green the eight applications of
09:32:50 the 11, in which they literally filed no substantive
09:32:55 response to a rejection. 8 of the 11 applications. Get a
09:32:59 rejection. File a new application. Get a rejection. File
09:33:03 a new application. You will see for over four years that's
09:33:07 what they said they did. The Federal Circuit has sort of
09:33:14 reinvigorated this doctrine of prosecution laches in Symbol
09:33:17 Technologies, about 15 years ago they talked about how this
09:33:20 doctrine had sort of died.

In Cancer Research they added an element or made
09:33:25 clear an element still existed, which is prejudice. To show
09:33:28 prejudice you have to show the accused or others were
09:33:30 invested in, worked on, or used the claimed technologies
09:33:34 during the period of delay.

09:33:36 You will hear evidence about that.

09:33:41 The '333 was called a pre-GATT patent. GATT was
09:33:47 passed in the mid-nineties and changed the way we calculate
09:33:49 patent terms, from 17 years from issuance to 20 years from
09:33:53 application. Because it's a pre-GATT patent, delay in
09:33:57 prosecution helps Shire. That way it expires 17 years after
09:34:01 it issues. The later it issues, the longer it lasts.

09:34:03 That's what drove the delay here, because Shire
09:34:06 benefits now keeping generics off the market rather than

09:34:10 early on when people are trying to develop drugs but the
09:34:13 early time for pharmaceuticals is less important than the
09:34:17 competition at the back end.
09:34:21 The evidence is going to show that Shire's
09:34:24 predecessor Hoechst spent four years doing nothing but
09:34:28 stalling on the prosecution. We are going to focus on the
09:34:33 Section 101 utility rejection. There is an office action on
09:34:40 August 17, 1990. The application that led to the '333 had
09:34:45 only what's called in vitro data in it. It had tests
09:34:48 outside live animals. The Patent Office said we don't
09:34:53 believe these drugs are actually bradykinin antagonists. We
want to see some in vivo data.
09:34:57 They first got that rejection in 1990. Your
09:35:00 Honor, the evidence is going to be they had the data. In
09:35:04 1990, they had it. I think by August 17, 1990 they had the
09:35:08 in vivo data, the evidence will show. When did they provide
09:35:12 it? Not until June 6, 1995.
09:35:16 They spent five years not providing the data.
09:35:19 First they argued, the first time they responded. They said
09:35:22 the in vitro data should be good enough. Maybe that's
09:35:26 legally right, maybe not. We are not really going to get
09:35:32 into that. We are not bringing a patent law expert into
09:35:34 that. Maybe it's good enough. Maybe not.
09:35:36 But they also had what the examiner specifically
09:35:39 said. Give me the in vivo data. Didn't do it. For four

09:35:42 years they didn't do it, they kept getting that rejection
09:35:45 over and over again, give me the in vivo data. Nothing. No
09:35:52 in vivo data. You see in 1995 they responded. Why in 1995
09:35:56 did they respond? Now GATT is coming. Now the GATT has
09:36:01 been passed and they know it is going to be 20 years from
09:36:05 application, not 17 years from initial filing, unless they
get the patent based on the application they have gotten.
09:36:11 Suddenly June 6, 1995, two days before the
09:36:14 effective date for GATT, they provide a substantive
09:36:17 response. And they provide the in-vivo data. And when they
09:36:21 provide the in vivo data, they do a declaration from one of
09:36:25 the inventors. He says, Thus, a compound that counteracts
09:36:28 the effect of bradykinin in vivo in an animal model can be
09:36:33 reasonably predicted to be effective in vivo in treating
09:36:37 asthma. The declaration provides the in-vivo data. What
09:36:40 happens? The Section 101 rejection goes away.
09:36:44 It's resolved.
09:36:46 You are going to hear from Mr. Raines. He is a
09:36:48 professor at MIT now. He was at the University of
09:36:55 Wisconsin. Previously on this issue, we talked about him a
09:36:58 little at the pretrial conference.
09:37:00 He is going to talk about the science in the
09:37:02 prosecution history. He is not a patent lawyer. He is not
09:37:07 an expert in patent law. And we are not offering him as
09:37:11 such. He will look at the prosecution history, look at the

09:37:12 declaration and the rejections, he will explain
09:37:17 scientifically what will be asked for, explain
scientifically what it is that Shire had, why they couldn't
09:37:20 have provided that data earlier. That will be the focus of
09:37:22 his testimony, not the prosecution history which you can
09:37:24 read through. Unfortunately, it is long. We will highlight
09:37:27 the right places. He will focus on the science behind it
09:37:31 and why Shire could have answered the scientific questions
09:37:38 earlier.

09:37:39 The answer to the question is, by 1990 they have
09:37:42 the data. They had even published the data. This is not a
09:37:47 situation where Shire or its predecessor ran new experiments
09:37:51 or had to test something else to ask the question. They had
09:37:55 it. There is no reason they couldn't have provided it in
09:38:00 1990, 1991, 1992, 1993, 1994.

09:38:06 In fact, they didn't provide the data before
09:38:08 they published it in an article they submitted in 1990 but
09:38:16 never gave it to the Patent Office until 1995. Had they
done so sooner, had they moved the prosecution along, the
09:38:19 patent would have issued earlier, and because it expires 17
09:38:21 years from issuance, it would expire earlier.

09:38:25 In fact, Your Honor, more likely than not, it
09:38:28 would be expired already. The patent expires in 2019 and
09:38:32 Shire has a regulatory exclusivity for Orphan Drug
09:38:37 Exclusivity through 2018. It is only that last year, even

though the last few years that makes a difference. If the prosecution were just one year less, we wouldn't be here because the patent wouldn't have actually any effect on Fresenius's intention to launch its product.

There is no explanation offered by Shire for this delay. We took the deposition of Dr. Wingefeld, she was one of the patent prosecutors from Sanofi. We asked over and over again, why didn't you provide the information earlier? I believe she will be here live. We asked her the last question, Why didn't Hoechst present the argument during remarks, Exhibit 26, in prior applications of the '333 prosecution?

That when they ultimately provide the answer, and said, why didn't you do that earlier? At the 30(b)(6), as the corporate designee, her answer," I don't know." That is unexplained delay. We asked her, tell us why. And we got, "I don't know."

With over four years of unexplained delay and prejudice, can we show prejudice? That is what happened in the Cancer Research case, if you look at the facts, the delay in prosecution was similar, but they lost because they hadn't shown prejudice.

Here we are showing just such evidence. You will hear that Dr. Stewart from the University of Colorado, that we talked about, he licensed his compounds to a company

09:40:05 called Nova Pharmaceuticals. Dr. Ron Burch was one of the
09:40:07 people who worked at Nova Pharmaceuticals at the time. He
09:40:11 is going to tell you the work that Nova was doing at the
09:40:16 time of the delay in the prosecution. He is going to
09:40:18 explain Nova was working on similar bradykinin antagonist
09:40:23 peptides. We are going to show you particular publications
09:40:26 from Nova that they focused on and a particular compound,
09:40:35 NPC 16731, one we talked about earlier, the NPC, that stands
09:40:39 for Nova Pharmaceuticals, there was a D-Tic in the 7
09:40:43 position and a Tic in the 8 position. That is a compound
09:40:47 Nova was working on the in the late eighties and early 90s.
09:40:53 That specific compound, Your Honor, is specifically claimed
09:40:54 in the '333 patent. It is not in the claim at issue, as an
09:40:56 unenforceability question we look at the patent as a whole,
09:40:56 like inequitable conduct.

09:40:59 What we see specifically is that even in Claim
09:41:01 12, that very compound that Nova was working on is claimed.

09:41:07 So Nova was working in this space. That's what
09:41:09 the Cancer Research case says is necessary for prejudice.

09:41:15 Now, Your Honor, we are going to make a second
09:41:18 prejudice argument, which is prejudice to Fresenius.

09:41:21 To be clear, Fresenius was not working on this
compound at the time.

09:41:27 If you look at Cancer Research carefully, what
09:41:30 it says is we are not going to let Barr, who was the generic

09:41:32 in that case, claim prejudice, for two reasons. One, Barr
didn't file its application at the earliest possible date,
09:41:42 on the NTE Minus 1 date, so the delay in approval is kind of
09:41:44 Barr's fault, not the brand's fault. Second, the brand by
09:41:47 delaying the prosecution didn't get the full five-year
09:41:52 patent extension you can get.
09:41:53 The undisputed evidence here and the undisputed
09:41:56 facts are that both of those things aren't true here.
09:41:59 Fresenius filed on the NCE-1 date. We filed the very first
09:42:05 day we could. Shire did get the five-year patent term
09:42:08 extension. The only reason that Fresenius can't get on the
09:42:12 market as soon as the regulatory exclusivity expires is the
09:42:16 '333 patent. For that, Fresenius can show prejudice.
09:42:22 What are we going to hear from Shire? Shire's
09:42:25 response is to call a patent lawyer, Dr. Ellis. She is
09:42:28 going to explain through the prosecution history that every
09:42:31 one of these steps, all these continuations and
09:42:34 continuations in part and various things they filed are
09:42:38 permitted under the rules. No dispute. True. If we look
09:42:41 at Symbol Technologies, the question on prosecution laches
09:42:47 isn't does this comply with the rules or not. We assume it
09:42:49 does. The question is, even if you comply with the rules is
09:42:52 the patent enforceable?
09:42:53 The testimony of Dr. Ellis quite frankly is
09:42:55 going to be mostly undisputed and mainly irrelevant because

09:42:59 it doesn't answer the question. She is not going to tell us
09:43:05 whether there was a delay, she is not going to tell us why
there was a delay, she is simply going to run through the
prosecution history, and we don't think that is necessary.
09:43:13 She is not going to engage the science.
09:43:13 In the end we think the delay of four years also
09:43:24 renders the patent unenforceable for prosecution laches.
09:43:35 Thank you.
09:43:36 THE COURT: Thank you, Mr. Wiesen.
09:43:39 MR. HAUG: Good morning, again, Your Honor.
09:43:52 May I approach, Your Honor?
09:43:55 THE COURT: Mr. Buckson will take that from you.
09:44:09 MR. HAUG: It is my pleasure to present an
09:44:11 opening statement on behalf of the plaintiffs Sanofi as well
09:44:17 as Shire.
09:44:19 I would like to put some context to this case if
09:44:23 I may, Your Honor.
09:44:23 Who are the parties here? Sanofi. Sanofi is a
09:44:28 global large pharmaceutical company, divisions in many
09:44:32 populations, research facilities all over the world. They
09:44:36 were formed from a combination of Sanofi, Synthelabo,
09:44:41 Hoechst, as well as Rhone-Poulenc.
09:44:45 They are involved in research and development of
09:44:47 many drugs which they bring to the market. In this
09:44:51 particular case, they are the owner of the patent, the '333

09:44:55 patent as we are calling it, which is called Peptides Having
09:45:02 Bradykinin Antagonist Action.
09:45:04 Shire, the other plaintiff, through an
09:45:06 acquisition, they acquired the rights to the product
09:45:11 Firazyr, which is a therapy, and they have an exclusive
09:45:18 license under the '333 patent.
09:45:20 Shire is also a pharmaceutical company, not
09:45:23 quite as large as Sanofi. However, a very significant,
09:45:27 substantial company, global company, large emphasis in rare
09:45:33 diseases, such as CNS disorders, and drugs.
09:45:37 I have here, I put a timeline up, if you start
09:45:41 at the bottom, 1989, the discovery of a series of bradykinin
09:45:57 antagonists began in the eighties. In 1989 they ultimately
09:46:00 filed a U.S. patent application, the first U.S. patent
09:46:03 application, covering all of that work they had done in
09:46:07 those discoveries.
09:46:08 They filed that in the U.S. on June 30, 1989.
09:46:14 As this timeline shows, the prosecution took
09:46:18 eight years until 1997 when the '333 patent issued. I think
09:46:29 for those people who are in this field and prosecuting
09:46:33 patents, particularly on new discoveries like this one, six,
09:46:39 seven, eight years is not ancient. It sounds like a lot of
09:46:44 years, but it really isn't.
09:46:46 You will hear evidence from people who were
09:46:48 involved in the prosecution of the patent as well as some of

09:46:50 the inventors.

09:46:51 The timeline goes on. After 1997, Hoechst, for
09:46:56 reasons that are not relevant to this case, decided they
09:47:00 would not continue commercialization of any of the icatibant
09:47:05 product and what happened was one of the lead inventors, Dr.
09:47:09 Knolle, Dr. Knolle was the head of chemistry for Hoechst at
09:47:14 the time, he was very much involved in the discovery of a
09:47:17 lot of these compounds, particularly, icatibant. He was
09:47:22 very disappointed when the company didn't continue with the
09:47:27 project, to the point where he left and he went to another
09:47:31 company called Jerini, another pharmaceutical company. What
09:47:35 happened was Jerini acquired the icatibant product as well
09:47:38 as rights to the '333 patent and they went ahead and
09:47:43 continued to develop the product. They went into clinical
09:47:46 trials for a good number of years. In fact, as this
09:47:49 timeline shows, in October of 2007 a New Drug Application,
09:47:55 an NDA, was submitted to the FDA by Jerini. That is now ten
09:48:01 years after the patent issued.

09:48:03 Jerini finally has the data to ask for marketing
09:48:06 approval for this drug.

09:48:08 Shortly thereafter, in 2008, Shire announces
09:48:10 that they buy Jerini, so that's how Shire becomes a
09:48:15 plaintiff in this case.

09:48:17 Shire continues to work on the product and it's
09:48:20 on August 25, 2011, the NDA is approved by the FDA for

09:48:27 **Firazyr.**

09:48:27 **When you look at the left, you see from drug**
09:48:31 **discovery to a final approval for a product to go to market**
09:48:36 **it took about 22 years. It is a long time, a lot of**
09:48:40 **development and expense and everything that goes into**
09:48:43 **developing a product. This is a poster child of what**
09:48:47 **happens for a new discovery going to the market eventually.**

09:48:50 **I should point out, the '333 patent, the claim**
09:48:54 **in this case is to a novel compound. It is not a**
09:48:58 **formulation. It is not that someone added a few more**
09:49:02 **ingredients and they made it more effective somehow. This**
09:49:05 **is a brand new compound that was discovered. Because of**
09:49:08 **that, it got approval in the end. And it's a wonderful drug**
09:49:12 **in the market, which I will get to in a second.**

09:49:17 **What is Firazyr? It is the branded name for**
09:49:21 **icatibant. Icatibant injection was approved by the FDA, as**
09:49:25 **I just said, in August of 2011. It is indicated for the**
09:49:30 **treatment of acute attacks of hereditary angioedema, HAE, it**
09:49:38 **is a rare genetic disease, a horrible disease. And here is**
09:49:43 **the product that is approved with a prefilled syringe, a**
09:49:48 **single dose, it can be self-administered. The key to this**
09:49:52 **drug is prior to icatibant you could not self-administer**
09:49:56 **subcutaneously a drug to treat HAE. Some of these other**
09:50:01 **drugs that my colleague pointed to, Berinert and Kalbitor,**
09:50:06 **for example, Berinert is an I.V. drug. You had to go to the**

09:50:10 hospital and it is a different active.

09:50:12 Kalbitor has a black box warning. It has safety
09:50:16 problems. It cannot be self-administered. Firazyr was the
09:50:21 first drug that you could self-administer for acute attacks
of HAE.

What is HAE?

09:50:30 One way to describe it is through pictures of
09:50:34 persons that have HAE. What you see here is a woman who is
09:50:36 suffering from an attack of HAE. It is uncontrolled
09:50:42 swelling. It can be facial, hands, feet, gastrointestinal,
09:50:49 anywhere in the body.

09:50:51 It is an acute attack. As you can see from this
09:50:54 picture, if it affects the larynx, it can be fatal. You
09:50:59 would not be able to breathe.

09:51:02 The hope is you would be able to treat a patient
09:51:07 who undergoes an attack that works quickly, effectively, and
09:51:13 can be administered quickly and effectively. Firazyr does
09:51:13 all of that.

09:51:14 There clearly was a long-felt need for this
09:51:18 drug. We are going to hear from Dr. Kaplan, who is a
09:51:23 well-respected clinician from the relevant time period,
09:51:26 about what that long-felt need was and how icatibant
09:51:30 satisfied that need.

09:51:32 I have another picture that shows the
09:51:34 progression of HAE in this page, if you will follow the

09:51:40 **Slides 1, 2, 3, 4, you can see how serious and how horrible**
09:51:45 **this disease is.**
09:51:47 **One more picture on the larynx, a little hard to**
09:51:50 **see on the black and white.**
09:51:52 **On the left is shown to be a normal larynx. You**
09:51:55 **can see the vocal chord as well as the trachea. You can't**
09:51:59 **see it that clearly on the right, that it is swollen. That**
09:52:03 **trachea is almost shut. If that is what happens to a**
09:52:07 **patient, it can be terminal to a patient.**
09:52:09 **The history of treatment of acute attacks of**
09:52:12 **HAE, there is no testimony -- you will hear testimony it**
09:52:17 **went all the way back to 1888. In 1888, we have when**
09:52:26 **Hereditary Angioneurotic Edema is identified in the medical**
09:52:28 **literature. It was a rare case back then, and no one knew**
09:52:32 **how to treat it. That was 1888.**
09:52:34 **It was not until 1989 that icatibant was**
09:52:38 **discovered and invented as an effective treatment.**
09:52:43 **As I earlier alluded to, the FDA approved two**
09:52:47 **other products, Berinert and Kalbitor in 2009. And in 2011**
09:52:53 **they approved the Firazyr product.**
09:52:58 **One last comment on what Firazyr is doing in the**
09:53:03 **marketplace. This is just a report from Cowen, which is**
09:53:11 **well-known among the analysts in the field.**
09:53:12 **If we just look at the last underlined sentence,**
09:53:16 **if I may, "The consultants think that such at home**

09:53:19 **administration of a subcutaneous drug is the 'holy grail' of**
09:53:24 **acute HAE treatments."**
09:53:29 **Commercially, Firazyr has been commercially**
09:53:33 **successful. On this slide I am slowing the sales of Firazyr**
09:53:38 **in 2016, which were in excess of a half a billion dollars.**
09:53:42 **As compared to Berinert, Kalbitor, and Ruconest in the**
09:53:47 **market, the sales are much, much higher and they are**
09:53:50 **increasing.**
09:53:51 **You will hear from Dr. Bell, who is an**
09:53:54 **economist, head of Life Sciences at Charles River**
09:53:57 **Associates, he will talk about the market and the commercial**
09:54:06 **success of Firazyr. Who is Fresenius? Fresenius is**
09:54:07 **the one who filed the ANDA. Your Honor is exceedingly**
09:54:12 **familiar with ANDA cases and has had many of them.**
09:54:16 **Fresenius filed their ANDA. They copied**
09:54:19 **icatibant. Because it is an active ingredient, you either**
09:54:23 **make it or you don't. There is no question of infringement**
09:54:26 **in this case because it's icatibant.**
09:54:29 **They filed it August 25th, 2015, with the**
09:54:33 **requisite Paragraph 4 certification, which is what is here.**
09:54:37 **Also, I should point out the FDA's stay of**
09:54:42 **approval, the 30-month stay doesn't expire for nearly a**
09:54:46 **year, February 25 of 2019.**
09:54:50 **As shown here, there are three dates. This case**
09:54:55 **is a little bit, in context from our view, on the right**

09:55:01 side, Firazyr, the Orphan Drug Exclusivity, it expires
09:55:04 August 25, 2018. What that means is because this is an
09:55:08 orphan drug, Shire got Orphan Drug exclusivity for a certain
09:55:13 period of time, which is a regulatory exclusivity, so there
09:55:15 can't be any generic version, if you will, the FDA won't
09:55:20 approve or give a final approval until at least August 25,
09:55:25 2018.

09:55:27 If we move to the left, I just mentioned, there
09:55:30 is an FDA stay of approval which goes out to February 25,
09:55:36 2019, about 30 months from that.

09:55:39 One more arrow to the left, the patent expires
09:55:43 July 15, 2019, 19 months from now.

09:55:50 I would like to talk about the patent.

09:55:53 The '333 patent, we are down to Claim 14. Claim
09:55:59 14, we are down to that because it is icatibant. It is a
09:56:03 peptide of that formula. As Mr. Wiesen has already pointed
09:56:06 out, it is a series of amino acids, it is a deca-peptide,
09:56:11 ten amino acids. And that is what Claim 14 is. I show here
09:56:16 right below the claim the chemical structure.

09:56:19 If I could have Claim 1 of the '333 patent,
09:56:32 right there it says what is claimed is a peptide of Formula
09:56:37 I, then it goes on, if you could please continue on with the
09:56:43 claim, if you look at the patent, it goes on for another
09:56:47 column, it goes on for two columns, it goes on for almost
09:56:53 three columns. That is the claim that was originally filed

09:56:57 and is granted.

09:56:58 Why is it so long? It's because the discovery
09:57:02 here was not just to icatibant. The discovery was a whole
09:57:05 class of bradykinin antagonists back in the 80s, compounds,
09:57:11 being one of those compounds of the many, many thousands of
09:57:15 compounds that are within the scope of the '333 patent. I
09:57:17 point this out because in this case Fresenius only wants to
09:57:22 talk about icatibant. And even their expert Raines wants to
09:57:27 just say this is how to get a patent on icatibant. When he
09:57:31 is looking at what happens in the Patent Office, he is doing
09:57:33 that doing that obviously in hindsight. And he is looking
09:57:37 back to 1991 and saying what could have, should have been
09:57:43 done to get a claim on icatibant earlier.

09:57:45 I am pointing out that at the time of the
09:57:47 prosecution and throughout the history of the prosecution,
09:57:50 it was not just about getting a claim on icatibant. It was
09:57:53 about getting a claim like this, Claim 1 that covers
09:57:56 thousands of compounds.

09:57:59 Obviously, they were entitled to it, they got
09:58:01 the patent on it. We cut the case down to only Claim 14
09:58:07 because that's all we need.

09:58:10 If we could go to the cover page of the patent,
09:58:20 the cover page of the '333 patent, the left-hand side, there
09:58:25 are nine inventors listed. They are all in Germany. Some
09:58:32 of them are no longer with us. This patent was filed back,

09:58:37 as I said, in 1989.

09:58:39 If we go down now where it says Related U.S.
09:58:44 Application Data, highlighted below that, what you see there
09:58:47 is a long list of continuation and continuation-in-part
09:58:53 applications. This is just the pedigree and the history of
09:58:57 this patent as it went through the Patent Office for that
09:59:01 eight years. It went through those refilings to do all
09:59:06 those different things.

09:59:08 Unfortunately, Your Honor, there is an
09:59:10 allegation here of patent prosecution laches, which requires
09:59:13 us to get into the patent prosecution and put forth why we
09:59:19 believe there is no undue delay.

09:59:21 There certainly was not any intent to delay. So
09:59:24 we have to get in the weeds on that.

09:59:27 It is a painful experience, I can tell Your
09:59:30 Honor in advance. I think it is necessary for the Court to
09:59:33 understand what happened in this prosecution and we will try
09:59:36 to do that as efficiently and quickly as possible.

09:59:42 In any event, there are a lot of applications
09:59:44 that were filed. Below that it says Foreign Application
09:59:47 Priority Date. There are five German priority documents.
09:59:52 When discoveries are made, they are filed in Germany first
09:59:56 because they are German companies and inventors, and they
10:00:00 combine them when they prosecute in the U.S.

10:00:03 These different applications are directed to

10:00:05 different claims, different discoveries. And they will
10:00:08 combine them. So the nine inventors listed here, they don't
10:00:13 all -- they are not all necessarily inventors on every claim
10:00:17 in this patent. They are different inventors that did
10:00:21 different things. And it is perfectly proper to put all
10:00:24 your inventors in one patent and do just what they did here.
10:00:29 My point here is that the '333 patent, while
10:00:34 it's only relevant for purposes of this litigation to
10:00:38 determine whether Claim 14 is valid and whether Claim 14 is
10:00:44 enforceable, I think there is context that is important
10:00:47 here.
10:00:48 The two issues to be decided, as Mr. Wiesen
10:00:59 said, two issues, obviousness-type double patenting and
10:01:05 prosecution laches. First, a word about history.
10:01:06 This case was filed in 2015. When filed it was
10:01:10 only about obviousness under 103. Mr. Wiesen talked about
10:01:15 the Stewart and Vavrek work that was out there, and his view
10:01:19 of what that prior art said and taught and therefore Claim
10:01:24 14 is invalid for obviousness.
10:01:27 We went through a lot of discovery on that.
10:01:31 After the pretrial order was filed, it was dropped. We are
10:01:36 happy it was dropped, of course. But it was dropped. That
10:01:39 is what that case is about. Whether or not Stewart, Vavrek,
10:01:43 all these people doing work out there, whether or not that
10:01:46 work rendered Claim 14 obvious, that is not an issue in the

10:01:50 case. What is now an issue in the case is obviousness-type
10:01:54 double patenting.
10:01:55 The claim now is that the '7,803, which I am
10:02:00 going to show you, is a later-filed patent, about three
10:02:05 years later. A later-filed patent for a different
10:02:09 invention. The argument is, this later-filed patent, as you
10:02:14 compare Claim 1 with Claim 14 of the earlier-filed '333
10:02:22 patent, makes the '333 patent Claim 14 obvious based on the
10:02:27 prior art.
10:02:28 What they are now arguing is we don't assert the
10:02:32 prior art renders Claim 14 obvious by itself, but when you
10:02:38 take the prior art together with the '7,803 Claim 1, somehow
10:02:44 that makes it obvious.
10:02:46 That's the case, as I understand it. I think
10:02:51 it's unusual even in the obviousness-type double patenting
10:02:56 arena because the reference patent, the '7,803 is later in
10:03:01 time than the '333 patent. The '333 patent prosecution
10:03:08 didn't even cite anything about the '7,803 patent. Well,
10:03:12 it's not prior art. The '7,803 claims are not only cited in
10:03:22 the '333 patent, right in the specification, but the Patent
10:03:27 Office rejected the '7,803 over the '333 patent, and Hoechst
10:03:32 had to prosecute and they actually had an interview in the
10:03:36 case. And they ultimately found, the Patent Office found,
10:03:40 that Claim 1 of the '7,803 was patentably distinct over the
10:03:46 '333 patent, and they are different inventions.

10:03:51 You will hear from an inventor of the '7,803
10:03:55 patent and you will of course hear from experts about the
10:03:59 differences between these claims.
10:04:08 Staying with obviousness for a second, what is
10:04:11 not in this case? Anticipation is not in the case,
10:04:15 inequitable conduct is not in the case, even though I heard
10:04:19 words from Mr. Wiesen this morning about stalling, trying to
10:04:22 delay. Those are heavy words. But there is no claim of
10:04:30 inequitable conduct here.
10:04:32 Hoechst was prosecuting this until 1997, then
10:04:37 they sold the product. They weren't even working on a
clinical program. They weren't even trying to get a drug to
10:04:45 market. Indeed, they decided they couldn't do that. So
10:04:48 they sold the product.
10:04:49 So the idea that from 1991 to 1995 they had some
10:04:54 motive to delay is simply unfounded. There is simply no
10:04:59 record or evidence in this record about that. Fresenius
chose not to take discovery of the patent attorneys handling
10:05:01 this case, Finnegan Henderson in Washington,
10:05:03 a well-respected patent prosecution firm. They took no
10:05:06 discovery of Hoechst or anybody else on the issue of
10:05:10 stalling or delaying, period. It's not in the case.
10:05:16 Prosecution laches, those of us in the patent
10:05:20 world for I will say now decades, if you had one prosecution
10:05:27 laches case, you are probably in the top one percent. It is

10:05:33 not something that you will see very often. The Federal
10:05:37 Circuit in the Lemelson case says that. It is a very, very
10:05:45 rare situation where we have patent prosecution laches. In
10:05:48 those days, the Federal Circuit was dealing with what we
10:05:53 call Lemelson cases. Lemelson became quite well known and
10:05:57 had a lot of notoriety because he was filing a lot of
10:06:02 patents and keeping them private, secret, we didn't have
10:06:07 publication rules back in those days, you didn't have to
10:06:10 publish your patent, you can stay in the Patent Office, no
10:06:14 one knew, for decades. Then technology would move along and
10:06:18 all of a sudden patents would start popping up. These were
10:06:23 called submarine patents and it was a real problem for the
10:06:27 laser industries and all kinds of industries.
10:06:29 Finally, the Federal Circuit said, that's
10:06:33 laches, you can't have patents pending for 20 years, 19
10:06:37 years, 10 years, 30 years, and so on. You are abusing the
10:06:42 patent system. That was abuse of the system.
10:06:47 Then there was there was a follow-on case,
10:06:50 Cancer Research, from 2010, from the Federal Circuit, the
10:06:54 Federal Circuit said, in addition to showing that the patent
10:06:59 applicant engaged in an egregious misuse of the statutory
10:07:03 patent system, quoting from the Symbol Technologies v.
10:07:07 Lemelson case, you have to show that a third party was
10:07:10 working in the field during the period of alleged delay and
10:07:13 that that third party had intervening rights and was

10:07:17 prejudiced by the delay.

10:07:18 The delay period here, the alleged delay period

10:07:22 here was 1991 to 1995.

10:07:26 Fresenius is urging the Court to find that it

10:07:30 was prejudiced. Fresenius didn't even know about this

10:07:33 product until it was approved in 2011. And we have

10:07:37 testimony in this case that will show Fresenius decided to

10:07:40 go after this product in 2014. This is 19 years after the

10:07:44 alleged period of delay. How that can be prejudice? I

10:07:48 think, as a matter of law, it can't. I think there is a

10:07:53 failure of proof as to this prong, but we will see when we

10:08:03 hear we hear the defendant's case.

10:08:04 I would like to go back to the '7,803 patent,

10:08:16 Claim 1. We are looking at Claim 1. It says a peptide of

10:08:22 the Formula I, then it has all of these different moieties

10:08:26 that appear into this compound or into this peptide.

10:08:33 Mr. Wiesen was correct. There is a claim

10:08:36 construction dispute, I think, because what I heard is

10:08:41 Fresenius saying, a peptide -- this claim doesn't require

10:08:46 everything that the claim says it requires. The claim says

10:08:49 a peptide of the Formula Z, P, A --

10:08:54 THE COURT: Say that again? Your interpretation

10:08:56 of what Mr. Wiesen said?

10:08:59 MR. HAUG: My understanding is that this claim

10:09:02 does not require all of the elements that appear here.

10:09:05 THE COURT: I didn't hear that.

10:09:08 MR. HAUG: I am sorry.

10:09:09 THE COURT: I just don't want to manufacture a dispute that is going to waste my time. Go ahead. Let's make this more of an opening, please.

10:09:23 MR. HAUG: In any event, Claim 1 here requires Z, which can be all of these different things. When any of those substituents appear as Z, that's what the compound is, it is a peptide, for example, all of these other things might be icatibant. And all these things can be something different than just icatibant.

10:09:52 If I can have DDX1-2.

10:10:04 This is a slide that is also shown. It is their version of the prosecution history. You will see this in various forms in this trial. It shows the complexity that was involved in this prosecution and the various applications that were filed for different reasons. Even as it shows here, it says Group 1, Group 2, Group 3. They were trying to claim "different things, and" we will try to help the Court walk through this application.

10:10:41 If I could have the one slide, 1.18. Here we have a timeline that shows the alleged period of delay, and as you see, the U.S. filing date was June of 1989. And the alleged period of delay is 1991 to 1995. And the patent issues in '97. You can see what happened thereafter.

10:11:12 Again, I think what will be important for the
10:11:15 Court is for the Court to see what effort there is of
10:11:22 intervening rights and prejudice.
10:11:24 With that, I will only very briefly say who we
10:11:29 have appearing --
10:11:30 THE COURT: I can see.
10:11:33 MR. HAUG: On Dr. Knolle, he does send his
10:11:36 regrets. He was going to be here as of Thursday. He had
10:11:41 emergency surgery this weekend.
10:11:44 THE COURT: Sorry to hear that.
10:11:46 Let's take a very short break.
10:11:49 (Recess taken.)
10:33:16 THE COURT: Your first witness.
10:33:18 MR. JAMES: Your Honor, Fresenius calls as its
10:33:22 first witness Dr. William Bachovchin.
10:33:58 ... WILLIAM BACHOVCHIN, having been duly sworn
10:33:59 as a witness, was examined and testified as follows...
10:34:10 THE COURT: Good morning, Doctor.
10:34:33 DIRECT EXAMINATION
10:34:34 BY MR. JAMES:
10:34:34 Q. Good morning, Dr. Bachovchin.
10:34:35 A. Good morning.
10:34:36 Q. Are you currently employed?
10:34:38 A. Yes, I am.
10:34:39 Q. Who are you currently employed by?

10:34:42 A. **I am employed by the Tufts University School of Medicine.**

10:34:46 Q. **What is your position at Tufts University School of Medicine?**

10:34:50 A. **I am a Professor in the Department of Developmental, Molecular, and Chemical Biology.**

Q. **What are your responsibilities in that position?**

A. **My responsibilities include teaching graduate**

10:35:02 **students, medical students and doing research.**

10:35:03 Q. **What subjects do you teach?**

10:35:05 A. **I teach amino acids, peptides and proteins, and I**

10:35:08 **teach a course in drug design.**

10:35:11 Q. **Dr. Bachovchin, have you prepared slides today to**

10:35:16 **accompany your testimony?**

10:35:17 A. **Yes, I have.**

10:35:18 Q. **Let's pick up the first slide, DDX2-2, using this**

10:35:24 **slide, just walk briefly through your educational**

10:35:27 **background?**

10:35:27 A. **I went to Wake Forest on a football scholarship and**

10:35:32 **got a Bachelor's degree in science and biology, and went on**

10:35:37 **to the California Institute of Technology and got a Ph.D.**

10:35:42 **degree in 1977.**

10:35:43 Q. **Did you do any postdoctoral work?**

10:35:45 A. **I did one year of postdoctoral work at the California Institute of Technology with Professor John D. Roberts, and**

then I did another year of postdoctoral work at the Harvard Medical School with Professor Bert Valee.

Q. After your work at Harvard, what did you do?

A. I accepted a position at Tufts School of Medicine as an assistant professor in the Department of Biochemistry.

Q. Dr. Bachovchin, in your binder is DTX-313 -- we will put it up on the face on the screen. Is DTX-313 a copy of your curriculum vitae?

A. Yes, it is.

Q. Does it accurately reflect your education and experience?

A. Yes, it does.

Q. We are focused on work going on prior to 1989. Can you tell us about the work going on at Tufts in 1989?

A. I was working on a class of enzymes known as proteases which degrade peptide bonds. I was working and studying their function and mechanism.

Q. We will talk more about this, but can you explain very briefly for us what a protease is?

A. Yes. A protease is an enzyme that will cut a peptide bond in a peptide or a protein and it can change the properties of the peptide. It can either degrade it, make it inactive or increase its activity.

Q. Can you explain what a peptide is?

A. A peptide is a polymer of amino acids bound together

10:37:24 like beads mixed linked on a string.
10:37:24 Q. During your time at Tufts, were there any particular proteases that you were working on?
10:37:29 A. Yes. I was working on a family of proteases, referred
10:37:32 to as the post-proline family of enzymes for their
10:37:35 preference for cleaving after proline bonds.
10:37:40 Q. What is proline?
10:37:41 A. Proline is a type of amino acid.
10:37:44 Q. Were you developing inhibitors for those enzymes?
10:37:48 A. I was.
10:37:48 Q. What does it mean to have an inhibitor of an enzyme?
10:37:52 A. An inhibitor of an enzyme blocks the enzyme
10:37:54 activities. It would prevent the enzyme, in this case the
10:37:59 protease, from cleaving the peptide bonds in the peptide
10:38:02 that was its substrate.
10:38:04 Q. What is the purpose of you making those inhibitors?
10:38:06 A. The purpose for making those inhibitors was twofold.
10:38:12 It was to use those inhibitors to help define and understand
10:38:16 the mechanism and function of the protease in vivo, but also
10:38:23 to try to find whether these inhibitors could be developed
10:38:26 as therapeutic agents.
10:38:28 Q. What is your current research focus at Tufts?
10:38:33 A. My current research continues to focus on post-proline
10:38:41 family proteases.
10:38:41 Q. Let's go back to DDX-2.2, that overview of your work.

10:38:43 **As the bottom there is a reference to a company called Point**
10:38:48 **Therapeutics. What's that?**
10:38:49 A. **Point Therapeutics is a company that I founded in 1999**
10:38:57 **and transferred some of the technology we developed of**
10:39:01 **inhibitors of proteases to develop further.**
10:39:03 Q. **Was Point Therapeutics developing drug products?**
10:39:07 A. **Yes, it was.**
10:39:07 Q. **What happened in the development of those drug**
10:39:11 **products at Point Therapeutics?**
10:39:13 A. **It took a compound that we had identified as an**
10:39:16 **inhibitor of one of these enzymes, it's called PDT-100 or**
10:39:22 **talabostat. That compound was taken into human clinical**
10:39:24 **trials and advanced to Phase III human clinical trials.**
10:39:28 Q. **Your curriculum vitae also mentioned Arisaph**
10:39:31 **Pharmaceuticals . Can you tell us about Arisaph?**
10:39:33 A. **Yes. That is a second company I founded in the same**
10:39:39 **way to develop some of the inhibitors we developed in my lab**
10:39:42 **for commercial development.**
10:39:44 Q. **How far did those inhibitors advance in development?**
10:39:46 A. **Two of the compounds we developed by ourselves were**
10:39:51 **taken by Arisaph into human clinical trials. One was an**
10:39:56 **inhibitor for a treatment of diabetes, and a second was a**
10:39:58 **treatment of cardiovascular disease.**
10:40:01 Q. **Other than your work at Tufts and your work with these**
10:40:05 **companies that you founded, have you held any other**

10:40:07 positions in your career?

10:40:08 A. Yes. For a long time I was a member of the outside --

10:40:13 THE COURT: Doctor, hold that thought just a second.

(Pause.)

10:42:28 BY MR. JAMES:

10:42:28 Q. Doctor, I believe the last question was other than your work at Tufts and founding these companies, have you

10:42:36 held any other positions in your career?

10:42:38 A. Yes. For a long time I was on the outside advisory committee of the Stable Isotope Committee Board of Los Alamos National Laboratory, and I served for ten years as

10:42:50 chairman of that committee.

10:42:50 Q. Can you very briefly describe your duties in that

10:42:53 position?

10:42:53 A. The responsibilities of that committee at Los Alamos

10:42:58 was the sole supplier of stable isotopes for chemical and

10:43:03 biological research. They would get requests from all over

10:43:06 the world for various labeled chemical entities. We would

10:43:10 evaluate these requests and help decide the priority of the

10:43:15 requests and help design ways in which those isotopes could

10:43:19 be incorporated into the molecules that would be requested.

10:43:25 Q. In addition to your work at Tufts and these

10:43:28 independent companies that you have mentioned, have you

10:43:29 consulted for any pharmaceutical companies?

10:43:31 A. **Yes, I have. I have consulted with DuPont, Merck,**
10:43:37 **Boehringer-Ingelheim, Cetus, and a number of others.**
10:43:38 Q. **Over what time span have you done that consulting**
10:43:41 **work?**
10:43:42 A. **That was from the early 1980s through the end of 1990.**
10:43:45 Q. **Was any of that work in peptide chemistry?**
10:43:48 A. **Essentially, all of it was in the area of peptide**
10:43:52 **chemistry.**
10:43:52 Q. **Have any of those companies that you mentioned funded**
10:43:56 **your research?**
10:43:57 A. **Yes, they did. I received funding from Merck,**
10:44:02 **Boehringer-Ingelheim and Cetus.**
10:44:03 Q. **How long has your research involved peptide chemistry?**
10:44:07 A. **My work has involved peptide chemistry essentially**
10:44:12 **from the beginning but certainly from the 1980s.**
10:44:15 Q. **Have you ever studied methods for making peptides more**
10:44:22 **resistant to enzymatic cleavage, that proteolytic cleavage**
10:44:26 **that you were mentioning earlier?**
10:44:28 A. **Yes.**
10:44:28 Q. **Can you describe that work?**
10:44:29 A. **We actually invented a new procedure for making**
10:44:32 **enzymes stable to degradation by proteases. We have made a**
10:44:37 **discovery that there was a single minor modification that**
10:44:40 **one could make to the amino acids in certain positions that**
10:44:47 **would render peptides that incorporated those amino acids**

10:44:51 **stable to all proteases in a certain class.**

10:44:54 Q. **Dr. Bachovchin, have you received any awards in**

10:45:01 **connection with your work in chemistry?**

10:45:02 A. **Yes. I received the Research and Development Award**

10:45:04 **from the National Institute of Health.**

10:45:06 Q. **Can you explain what that award is?**

10:45:09 A. **That is an award to fund my full salary for five years**

10:45:14 **to allow me to focus 100 percent of my time on research.**

10:45:18 Q. **Have you received any grants as part of your work?**

10:45:21 A. **Yes, I have. I have received numerous grants from**

10:45:22 **both the NIH and the National Science Foundation.**

10:45:26 Q. **Have any of those grants related to peptide chemistry?**

10:45:29 A. **Essentially all of them have.**

10:45:30 Q. **Have you published any articles in connection with**

10:45:34 **your work?**

10:45:34 A. **Yes, I have. I have published more than 100 articles.**

10:45:38 Q. **Are you a named inventor on any patents?**

10:45:41 A. **Yes, I am. I am a named inventor on more than 40**

10:45:44 **issued U.S patents and more than 100 patents around the**

10:45:49 **world.**

10:45:49 Q. **Have you served as a reviewer related to any journals**

10:45:53 **related to peptide chemistry or drug development?**

10:45:56 A. **Yes, I have. I served as a reviewer for Nature,**

10:45:59 **Science, Proceedings for the National Academy of Science,**

10:46:02 **Journal of Medicinal Chemistry, Biochemistry, the Journal of**

10:46:08 **the American Chemical Society, and several others.**

10:46:09 **MR. JAMES: Your Honor, Fresenius offers Dr.**

10:46:12 **Bachovchin as an expert in the field of peptide chemistry,**

10:46:15 **drug design and discovery.**

10:46:17 **THE COURT: Any objection?**

10:46:18 **MS. KUZMICH: No objection, Your Honor.**

10:46:20 **THE COURT: The doctor is accepted as an expert**

10:46:22 **in those fields.**

10:46:23 **BY MR. JAMES:**

10:46:24 Q. **I want to turn to your opinions in this case, Doctor.**

10:46:28 **You understand that the '333 patent is at issue in this case**

10:46:33 **here?**

10:46:33 A. **Yes.**

10:46:34 Q. **Have you reviewed that patent?**

10:46:35 A. **Yes.**

10:46:35 Q. **What claim are you offering an opinion about?**

10:46:39 A. **It's Claim 14.**

10:46:40 Q. **Let's put that out on the screen. That is DDX2-3. We**

10:46:46 **will come back to this. At a high level, what is in Claim**

10:46:51 **14 of the '333 patent?**

10:46:52 A. **Claim 14 claims a specific ten-amino acid peptide, the**

10:47:03 **sequence shown there by the three letters for amino acids.**

10:47:03 Q. **Let's put up DDX2-4. What issue were you asked**

10:47:10 **address in this case?**

10:47:10 A. **I was asked whether Claim 14 of the '333 patent is**

10:47:15 **invalid for obviousness-type double patenting over Claim 1**
10:47:19 **of the '7,803 patent.**
10:47:21 Q. **In that regard, can you tell us the question that you**
10:47:27 **addressed?**
10:47:28 A. **Yes, the question I addressed was, is Claim 14 of the**
10:47:33 **'333 patent an obvious variant of Claim 1 of the '7,803**
10:47:39 **patent.**
10:47:39 Q. **Have you formed an opinion on that question?**
10:47:44 A. **Yes, I have. My opinion is that Claim 14 of the '333**
10:47:51 **patent is an obvious variant of Claim 1 of the '7,803**
10:47:59 **patent.**
10:47:59 Q. **Have you summarized the basis for that opinion in a**
10:48:03 **slide?**
10:48:03 A. **I have.**
10:48:04 Q. **Let's look at the next slide. Using this slide, Dr.**
10:48:08 **Bachovchin, can you explain to the Court the basis for your**
10:48:11 **opinion that Claim 14 of the '333 patent is invalid for**
10:48:15 **obviousness-type double patenting?**
10:48:17 A. **Yes. The reasons include that the '7,803 patent and**
10:48:21 **the '333 patents are co-owned and have inventors in common.**
10:48:26 **Also, peptides claimed in the '7,803 patent include the same**
10:48:33 **ten-amino-acid sequence recited in Claim 14 of the '333**
10:48:36 **patent, with a removable protecting group attached.**
10:48:41 **And a person of skill in the art would have been**
10:48:43 **motivated to remove the protecting group, and would have**

10:48:46 **reasonably expected the resultant peptide to be a bradykinin**
10:48:50 **antagonist.**
10:48:51 **For these reasons I conclude that the peptide of**
10:48:55 **Claim 14 of the '333 patent is an obvious variant of Claim 1**
10:49:01 **of the '7,803 patent.**
10:49:04 Q. **Let's turn to the definition of the person of ordinary**
10:49:08 **skill in the art. In your analysis, did you use a**
10:49:11 **definition of the person of ordinary skill?**
10:49:13 A. **Yes, I did.**
10:49:14 Q. **Let's put up the next slide. What is shown on Slide**
10:49:21 **DDX2-6?**
10:49:23 A. **What is shown here is my definition of the person of**
10:49:26 **ordinary skill in the art.**
10:49:27 Q. **What qualifications would a person of ordinary skill**
10:49:31 **in the art have had under your definition?**
10:49:33 A. **Under my definition, a person of ordinary skill in the**
10:49:37 **art would be one who had a Ph.D. in organic chemistry,**
10:49:41 **medicinal chemistry, pharmacology, or a related field, and**
10:49:44 **had years of experience in medicinal chemistry or**
10:49:47 **pharmacology related to peptides and experience developing**
10:49:51 **new potential drug candidates.**
10:49:54 Q. **In your opinion, are there any other characteristics**
10:49:56 **that the person of ordinary skill in the art would have had?**
10:49:59 A. **Yes. I believe that person of skill in the art would**
10:50:03 **also have regularly reviewed the literature related to**

10:50:06 organic chemistry and medicinal chemistry, including peptide
10:50:09 chemistry, and would have been able to analyze and
10:50:12 characterize potential drug compounds both structurally and
10:50:16 with regard to their biological properties.
10:50:18 Q. Do you understand that the plaintiffs in this case
10:50:21 claim a priority date for the '333 patent of January 1989?
10:50:26 A. Yes, I do.
10:50:27 Q. Would you personally have fit the definition of a
10:50:31 person of ordinary skill in the art as of January 1989?
10:50:35 A. Yes, I would have.
10:50:36 Q. Do you understand that the experts for the plaintiffs
10:50:38 have asserted a slightly different definition for the person
10:50:42 of ordinary skill in the art?
10:50:43 A. Yes.
10:50:43 Q. Would your opinions in this case be altered if the
10:50:47 Court were to adopt the plaintiffs' definition of the person
10:50:50 of ordinary skill in the art?
10:50:51 A. No, it would not.
10:50:52 Q. I want to turn now and talk about the technical
10:50:56 background in this case.
10:50:57 You mentioned earlier that peptides are made up
10:51:01 of amino acids. And I want to start there. Let's pull up
10:51:05 DDX2-7. What is shown on this slide?
10:51:09 A. This slide shows the generic structure of the amino
10:51:12 acid.

10:51:12 Q. **On the left side of this slide you have a blue box. What is in that blue box?**

10:51:15 A. **All amino acids have an amino group and an acid group. That's what gave them their name.**

10:51:21 **And the blue box shows the amino group. The amino group is composed of a nitrogen atom and two hydrogen atoms.**

10:51:23 Q. **And in the red box what is depicted?**

10:51:32 A. **That shows the acid part, in this case it is a carboxylic acid group, a carboxylic group is composed of a carbon group, two oxygen atoms and a hydrogen atom.**

10:51:36 Q. **In the middle there is an orange box with an R in it. What's that?**

10:51:41 A. **That is referred to as the side chain. And it is the side chain that gives each amino acid its specific characteristics and distinguishes one amino acid from another.**

10:51:45 Q. **The next slide, DDX2-8, what is illustrated here?**

10:51:51 A. **This illustrates how the R groups can vary from one amino acid to another. You can see each one has a carboxylate group and an amino group, but they differ in their side chains.**

10:51:51 Q. **Starting with the amino acid on the left, can you explain the R group or side chain of glycine?**

10:52:04 A. **So the side chain of the amino acid on the left, which**

10:52:04

10:52:09

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10:52:35 **is glycine, is illustrated in orange. You can see, it**
10:52:39 **consists only of a hydrogen atom. Glycine is the smallest**
10:52:44 **and simplest of the amino acids.**
10:52:46 Q. **With respect to arginine, can you explain its side**
10:52:50 **chain?**
10:52:51 A. **You see the side chain of arginine, indicated here in**
10:52:56 **orange, is much larger. It has a chain of carbon atoms**
10:53:00 **connected together and ends with a grouping we refer to as a**
guanidine group.
Q. **Would you next talk about the side chain of**
phenylalanine?
10:53:11 A. **Phenylalanine is referred to as an aromatic side chain**
or an aromatic amino acid. That's because of this
10:53:20 **six-membered ring, where you see there the double bond, it's**
10:53:20 **these double bonds together, that free structure, that**
10:53:22 **refers to the aromatic character on the side chain.**
10:53:26 Q. **The amino acid on the far right, proline, I think you**
10:53:30 **mentioned that earlier. Its side chain looks a little**
10:53:34 **different. Can you explain that?**
10:53:36 A. **Proline is unusual. It's the only amino acid whose**
10:53:39 **side chain bends around and forms a bond to the amino group,**
10:53:45 **the backbone amino group.**
10:53:47 Q. **In common parlance, how many naturally occurring amino**
10:53:53 **acids are there?**
10:53:53 A. **In common parlance, there are 20 naturally occurring**

10:53:56 **amino acids.**

10:53:57 Q. **The next slide, what is shown herein?**

10:54:01 A. **This is showing all 20 naturally occurring amino**
10:54:04 **acids.**

10:54:04 Q. **Can you talk about how they vary from one another?**

10:54:07 A. **You can see on the top left glycine, which we talked**
10:54:11 **about, glycine is the smallest and simplest one.**

10:54:14 **The next one up from that is alanine. Alanine**
10:54:18 **differs in that it has a methyl group. As you go to the**
10:54:22 **right and towards the bottom, you run into big and more**
10:54:27 **complicated side chains.**

10:54:28 Q. **For the record, that is DDX2-9.**

10:54:33 **Let's look at the next slide. What are you**
10:54:38 **showing on DDX2-10?**

10:54:42 A. **This is illustrating that amino acids can exist in two**
combinations referred to as stereoisomers. And we are using
10:54:52 **alanine to illustrate these stereoisomers.**

10:54:52 Q. **You have them labeled on the left L-alanine and on the**
10:54:57 **right D-alanine. Can you explain the difference in these**
two?

10:55:00 A. **The L-alanine nomenclature refers to the juxtaposition**
10:55:05 **in space of the groups attached to the central carbon atom.**
10:55:09 **Here we see the central carbon atom is labeled in yellow.**
10:55:13 **And you have four groups that attach to that carbon atom.**
10:55:16 **But these four groups can be attached in two ways such that**

10:55:21 these two groups cannot be superimposed in space. They are
10:55:28 non-superimposable mirror images, much like your right hand
10:55:30 and your left hand. You have the same fingers, the same
10:55:32 thumb, but they cannot be superimposed. They are mirror
10:55:36 images. This is true of the L and D forms of amino acids.
10:55:42 Q. This difference between L and D amino acids, Dr.
10:55:47 Bachovchin, is that important in this case?
10:55:49 A. Yes, it is.
10:55:50 Q. Why is that?
10:55:51 A. That is because the compound at issue in this case
10:55:58 incorporates a number of D-amino acids into the peptide
10:56:03 sequence.
10:56:04 Q. How are amino acids joined together into a peptide,
10:56:09 Doctor?
10:56:09 A. Amino acids are joined together in a peptide by the
10:56:12 formation of peptide bonds.
10:56:14 Q. Let's look at the next slide, that's DDX2-11. Can you
10:56:20 use this slide to talk about how a peptide bond is formed?
10:56:24 A. Yes. This illustrates two amino acids and highlights
10:56:28 the carboxylic group of one amino acid and highlights the
10:56:34 amino group of another. A peptide bond is formed when these
10:56:37 two groups come together and form a peptide bond.
10:56:42 Q. Let's put up the rest of the slide.
10:56:47 Can you explain what is shown on the right-hand
10:56:50 side of DDX2-11?

10:56:52 A. **This shows these two groups have come together and**
10:56:55 **formed a peptide bond. When that happens, water is**
10:57:00 **eliminated.**
10:57:01 Q. **You have this labeled as a dipeptide, why is that?**
10:57:05 A. **Yes, it is staple nomenclature to use a prefix to**
10:57:10 **designate the length of the peptide polymer. In this case**
10:57:14 **it is a dipeptide because there are two amino acids. If**
10:57:17 **there are three, it would be a tripeptide, if there were**
10:57:21 **four, it would be a tetrapeptide.**
10:57:24 Q. **When you are talking about making peptide bonds, can**
10:57:31 **that process go in reverse?**
10:57:32 A. **Yes.**
10:57:32 Q. **Are there molecules in the body that would facilitate**
10:57:36 **that reverse process?**
10:57:37 A. **Yes, they can.**
10:57:37 Q. **What kind of molecules are those?**
10:57:39 A. **They are often referred to as hydrolytic enzymes,**
10:57:44 **because they are adding water, the reverse reaction is**
10:57:47 **adding water. They are often referred to as hydrolytic**
10:57:51 **enzymes or proteolytic enzymes, because of the protease.**
10:58:08 Q. **I want to talk a little bit about how chemists write**
10:58:11 **out peptide sequences. Let's look at the next slide.**
10:58:16 **At the top, you have something labeled a**
10:58:19 **bradykinin. Can you explain what you're illustrating**
10:58:22 **there?**

10:58:22 A. **Yes. So this is illustrating a peptide that is known**
10:58:29 **as bradykinin, and this shows the amino acid sequences that**
10:58:32 **define the sequence of bradykinin.**
10:58:35 Q. **Now, on the left-hand side of bradykinin, you have a**
10:58:39 **label N-terminus. Can you explain that?**
10:58:43 A. **Yes. So the amino acid that's at the N-terminus has**
10:58:49 **been linked to the next amino acid of the carboxyl group,**
10:58:53 **but this amino group is free, not bound to anything. That's**
10:58:56 **indicated here by the presence of this NH2 group highlighted**
10:58:59 **in yellow. So we refer to this as the N-terminal amino**
10:59:03 **group.**
10:59:03 Q. **And on the far right you have the C-terminus labeled.**
10:59:07 **Can you explain that, please?**
10:59:08 A. **Yes. So again this is -- on this end of the molecule,**
10:59:12 **the last amino acid would be a carboxylate group, and here**
10:59:15 **this indicates that this carboxylate group is present and**
10:59:18 **unbound to anything else, and we refer to this as the**
10:59:22 **C-terminus.**
10:59:25 Q. **Could you put up the rest of that slide.**
10:59:28 **Below the bradykinin sequence you have two**
10:59:30 **additional sequences there, Dr. Bachovchin. Could you**
10:59:33 **explain those, please?**
10:59:34 A. **So this is alternate ways of illustrating this**
10:59:38 **ten-amino-acid peptide sequence. You can -- the yellow**
10:59:42 **highlighting here indicates that you have the amino group**

10:59:44 and the carboxylate group on the N-terminus and C-terminus
10:59:50 respectively. But you can also write it by omitting those
10:59:53 and by convention it's understood that this peptide has the
10:59:59 free amino group on the N-terminus and free carboxylate
11:00:03 group on the C-terminus.
11:00:03 Q. You provided some numbers underneath those sequences.
11:00:06 Can you explain those numbers, please?
11:00:08 A. Yes. By convention, amino acid sequences in
11:00:11 polypeptides and proteins are by convention numbered
11:00:14 sequentially from the N-terminus to the C-terminus. So in
11:00:19 the case of a nine-amino-acid peptide, the amino acid at the
11:00:23 N-terminus would be number one and the amino acid at the
11:00:26 C-terminus would be number nine.
11:00:28 Q. Dr. Bachovchin, we'll come back and talk about this in
11:00:31 more detail later, but in the 1980s, were researchers making
11:00:34 bradykinin analogs?
11:00:35 A. Yes, they were.
11:00:39 Q. Can you explain to the Court what a bradykinin analog
11:00:42 is?
11:00:42 A. A bradykinin analog would be a peptide based on the
11:00:46 structure of bradykinin, but to which certain changes were
11:00:49 made to make it a little different than bradykinin.
11:00:53 Q. Let's look at the next slide. And at the top of this
11:00:57 slide you've written, substitution of an amino acid. Can
11:01:01 you explain what you are showing there?

11:01:02 A. **Right. So one way of making a bradykinin analog would**
11:01:06 **be to substitute one of the amino acids for another. And so**
11:01:10 **here we're showing that bradykinin itself has a serine at**
11:01:14 **position six. So if we made another peptide and put a**
11:01:18 **glycine down in that position instead of a serine, we would**
11:01:21 **have an analog of bradykinin.**
11:01:23 Q. **And how would that analog be noted in a paper or**
11:01:29 **publication, for example?**
11:01:31 A. **So an analog of a peptide is designated as we've shown**
11:01:37 **here. What you do is you put a parentheses and you indicate**
11:01:40 **what changes have been made to the starting molecule.**
11:01:43 **So this says that -- this is bradykinin, but**
11:01:47 **it's bradykinin that has a glycine at the six position**
11:01:50 **instead of whatever was at the position to start with. This**
11:01:53 **makes it easy to understand what peptide it is. You don't**
11:01:57 **have to go through and confirm each time that this is a**
11:02:00 **bradykinin analog. This tells you it's a bradykinin analog**
11:02:04 **with glycine at the six position.**
11:02:05 Q. **Let's put up the next part of the slide, Mr. Chase.**
11:02:09 **Here you've labeled it addition of an amino acid. Can you**
11:02:12 **explain that?**
11:02:12 A. **So another way to modify a starting sequence, to make**
11:02:16 **an analog of a starting sequence, would be to add an amino**
11:02:21 **acid. In this case we are adding an amino acid to the**
11:02:24 **N-terminus.**

11:02:26 Q. **All right. And what amino acid is being added at the**
11:02:31 **N-terminus?**
11:02:32 A. **In this case we're adding a D-Arginine to the**
11:02:37 **N-terminus.**
11:02:37 Q. **How would you write that out?**
11:02:38 A. **To indicate that this is a bradykinin analog with**
11:02:40 **D-Arginine at the N-terminus, we would put in front of it**
11:02:46 **BK -- that stands for bradykinin. In parentheses we say**
11:02:50 **D-arg at position zero, bradykinin.**
11:02:54 Q. **Can you explain why you designated as position zero**
11:02:58 **and not one?**
11:02:58 A. **This is designated as position zero to be consistent**
11:03:01 **with the numbering of starting peptide bradykinin so we**
11:03:04 **don't have to change the numbering of the starting peptide.**
11:03:07 **The starting peptide retains its numbering, and we've**
11:03:10 **continued numbering to the left going to zero and eventually**
11:03:13 **to negative numbers.**
11:03:15 Q. **The D that's modifying the arginine there, is that the**
11:03:20 **D and L designation we talked about earlier?**
11:03:22 A. **Yes, it is. That indicates that that is D-Arginine,**
11:03:25 **the non-natural stereoisomer of arginine.**
11:03:28 Q. **The other amino acids are not labeled D or L. What**
11:03:31 **would be the understanding with respect to those amino**
11:03:34 **acids?**
11:03:34 A. **So if you don't see a D or an L in front of an amino**

11:03:38 acid, the conventional understanding is that those amino
11:03:40 acids are in the L configuration or the naturally occurring
11:03:43 configuration.
11:03:44 Q. Are D-amino acids natural amino acids?
11:03:48 A. D-amino acids are not natural amino acids.
11:03:52 Q. Can these examples of addition and substitution, can
11:03:55 they be combined?
11:03:56 A. Yes, they can.
11:03:57 Q. Let's put up the last part of the slide, Mr. Chase.
11:03:59 And using that last part of the slide, Doctor, could you
11:04:02 explain that concept?
11:04:03 A. Yes. So here we're illustrating that these two
11:04:07 substitutions, these two changes, these two modifications
11:04:10 are being made to the bradykinin molecule. So we're taking
11:04:14 the serine position six and changing it to a glycine and
11:04:17 we're adding arginine to the N-terminus. So this would be
11:04:21 designated as a bradykinin analog, in parentheses to
11:04:25 illustrate that this is bradykinin, but with D-Arginine in
11:04:28 position zero and with glycine at position six.
11:04:32 Q. How are these concepts relevant to icatibant?
11:04:35 A. They are relevant to Oic because icatibant is
11:04:39 basically an analog of bradykinin in which various amino
11:04:44 acids have been substituted or added.
11:04:46 Q. I'd like to turn now to the concept of peptide
11:04:51 synthesis. Were there known methods for synthesizing

11:04:55 **peptides in January 1989?**

11:04:56 A. **Yes, there were.**

11:04:58 Q. **By 1989, what was the most common method for**

11:05:01 **synthesizing peptides?**

11:05:02 A. **By 1989, the most widely used method for synthesizing**

11:05:07 **peptides was a method referred to as solid phase peptide**

11:05:11 **synthesis.**

11:05:11 Q. **I want to talk a little bit more about this. In your**

11:05:16 **binder is DTX-182. We'll put up the face page.**

11:05:20 **Doctor, is this a copy or an excerpt from a**

11:05:24 **textbook by Bodanszky?**

11:05:26 A. **Yes, it is.**

11:05:27 Q. **When was Bodanszky published?**

11:05:32 A. **Bodanszky was published in 1988.**

11:05:34 Q. **Was the Bodanszky textbook a well-known text before**

11:05:37 **1989?**

11:05:38 A. **Yes, it was.**

11:05:39 Q. **Let's put up an excerpt from page DTX-182.009.**

11:05:48 **There's a paragraph there that starts with the word yet.**

11:05:51 **Can you explain to the Court what Bodanszky is saying**

11:05:53 **here?**

11:05:54 A. **Yes. Bodanszky is basically saying here that the most**

11:05:56 **important development in the history of peptide synthesis**

11:06:00 **was the invention of solid phase peptide synthesis by**

11:06:04 **Merrifield in 1963.**

11:06:07 Q. **Why was solid phase synthesis such an important development?**

11:06:10 A. **It was an extremely important development because it greatly facilitated the production of peptides for a number of reasons, not the least because it allowed for the automation of peptide synthesis such that you could make an amino acid with a machine that would pretty much do the work for you by punching in the peptide synthesis peptide sequence.**

11:06:33 Q. **You said that you could make an amino acid by punching in a peptide sequence?**

11:06:38 A. **I'm sorry. Peptide. You could make a peptide automatically by instructing the machine to make the peptide.**

11:06:45 Q. **Thank you.**

11:06:47 **I want to talk about an example of how solid phase synthesis would work. Let's go to the next slide, which is DDX-2-16.**

11:06:56 **Can you tell us what you are showing here, Dr. Bachovchin?**

11:07:00 A. **So here we have an illustration. We're saying that if we desire to make this five amino acid peptide sequence here labeled one through five on the N-terminus to C-terminus, how we would do that with solid phase peptide synthesis.**

11:07:13 Q. **Let's go to DDX-2-17. Can you explain what you are**

11:07:17 showing here, Doctor?
11:07:18 A. So this shows that the solid phase peptide synthesis
11:07:23 used something like the column that's packed with here,
11:07:26 we're calling resin beads, which are basically an insoluble
11:07:30 material, and it's packed into the column. And you could
11:07:35 add things to the top and remove things from the bottom.
11:07:38 Q. Okay. We've added some more text here in DDX-2-18.
11:07:44 It says, protected amino acid. Can you tell us what you are
11:07:47 showing in this slide?
11:07:48 A. Yes. So here we're showing that to these resin beads
11:07:52 in this column, we are now adding a solution containing a
11:07:55 protected amino acid.
11:07:57 Q. Let's put up just a little bit more here, Mr. Chase.
11:08:01 If you could put up the next part of the slide, DDX-2-19 and
11:08:06 stop there.
11:08:07 Dr. Bachovchin, what are you showing in
11:08:11 DDX-2-19?
11:08:12 A. This is showing an expanded view of one of the resin
11:08:15 beads.
11:08:15 Q. Let's go to the next slide and stop there.
11:08:19 Now, Dr. Bachovchin, you have a couple of
11:08:23 colored circles and a block there. Can you explain what you
11:08:26 are showing in DDX-2-19 here?
11:08:28 A. Yes. This is designed to illustrate an amino acid
11:08:31 that we're adding to the solid phase resin through this

11:08:34 column, and this is amino acid number five. And you can see
11:08:38 amino acid number five is here designated in blue and its
11:08:42 N-terminus has got an orange group on it, and we're using
11:08:46 this orange group to designate that that N-terminus has a
11:08:49 protecting group on it. But the C terminal carboxylate
11:08:53 group is free.
11:08:53 Q. So you said the N-terminus is protected. That's the
11:08:57 amino group that we talked about earlier?
11:09:00 A. Yes. The amino group on the N-terminus has got a
11:09:04 blocking or protecting group on it to prevent it from
11:09:08 participating in unwanted reactions.
11:09:11 Q. That protecting group, is that a chemical?
11:09:13 A. Yes, it is.
11:09:14 Q. Let's go forward with the slide. Dr. Bachovchin, can
11:09:21 you explain what we're seeing there?
11:09:23 A. So what we're illustrating here is this first amino
11:09:26 acid which we're labeling amino acid five, the C terminal
11:09:30 amino acid, forms a bond to the solid resin.
11:09:33 Q. Why did you start with amino acid five?
11:09:36 A. Because solid phase synthesis goes in the reverse
11:09:39 direction from the nomenclature of peptides from N-terminus
11:09:43 to C-terminus. In solid phase peptide synthesis, we make
11:09:48 peptides from the C-terminus to the N-terminus.
11:09:50 Q. Okay. I want to step back for a second and ask you
11:09:53 about that protecting group. Do protecting groups play a

role in this litigation?

A. Yes, they do.

Q. Can you explain that?

A. They play a very important role because the issue at stake is whether a peptide with and without a blocking group on the N-terminus constitute different peptides or is one an obvious variant of another.

Q. Let's look at the next part of the slide, and here you have some amino acid five. Can you explain what's happening here, Dr. Bachovchin?

A. So this is designed to illustrate what would happen in the absence of a protecting group, and you can see what would happen is amino acid five would form uncontrolled polymers on the beads, but it would also form uncontrollable mixtures of dipeptides, tripeptides and higher amino acids in the solvent space between the rest of the beads. Basically, you would have lost any control of making the desired peptide sequence.

Q. Let's look at the next slide, which is DDX-2-21. Dr. Bachovchin, what are you illustrating on this slide?

A. So this is illustrating that every resin bead would form multiple bonds with the C terminal amino acid, which in this case is amino acid five, and even after that, you would still have amino acids, blocked amino acids free in the space between the resin beads.

11:11:27 Q. **Let's go back now and look at that single amino acid**
11:11:31 **you had attached. That's DDX-2-22. What's the next step in**
11:11:37 **the solid state synthesis process?**
11:11:40 A. **Well, after washing the way the blocked, unbound amino**
11:11:43 **acids, the next thing you would do would be to deprotect the**
11:11:47 **N-terminus.**
11:11:49 Q. **Why do you have to deprotect the N-terminus?**
11:11:51 A. **Because you're getting ready now to add the next amino**
11:11:55 **acid in the sequence and you need to have this amino group**
11:11:59 **out free so that it can couple to the next amino acid.**
11:12:03 Q. **Let's look at the next slide.**
11:12:06 **And, Dr. Bachovchin, just for the record,**
11:12:10 **DDX-2-22, what are you showing there?**
11:12:11 A. **So this is showing now that the protecting group has**
11:12:15 **been removed and washed away, and so now you have the amino**
11:12:19 **acid number five attached to the resin bead, but now the**
11:12:23 **amino group on this amino acid is free and available to do**
11:12:28 **chemistry with the next amino acid.**
11:12:30 Q. **What's the next step in the process?**
11:12:32 A. **The next step would be to add the next amino acid in**
11:12:37 **sequence if you want the bead in the next position as the**
11:12:43 **N-terminal protected amino acid.**
11:12:45 Q. **Let's look at the next slide. This is DDX-2-23.**
11:12:50 **Mr. Chase, if you could just let that roll a little bit.**
11:12:53 **And, Dr. Bachovchin, can you tell us what we're**

11:12:55 **seeing here?**

11:12:56 A. **Yes. And here this is showing now that we're adding**
11:12:58 **the next amino acid, amino acid four, and you can see amino**
11:13:04 **acid four has a free carboxylate group, but it has an**
11:13:07 **N-protecting group on the N-terminus. Again, very crucial**
11:13:11 **it has that protecting group. But now the only thing that**
11:13:14 **can happen is the carboxylate group can react with this**
11:13:18 **amino group and you prevent this amino group from**
11:13:23 **participating inside this reaction illustrated here.**

11:13:24 Q. **Every time you add an amino acid, do you have to take**
11:13:27 **that protecting group off?**

11:13:28 A. **Yes. Every time you add an amino acid, you have to**
11:13:32 **take the protecting group off.**

11:13:33 Q. **Now, Mr. Chase, if you could just let the animation**
11:13:38 **run.**

11:13:38 **And, Dr. Bachovchin, if you could just tell the**
11:13:40 **Court what you are showing in this animation?**

11:13:43 A. **So in order to make your desired peptide sequence,**
11:13:46 **what you do, you run through cycles of deprotection, wash**
11:13:49 **away the extraneous materials of the column, add the next**
11:13:54 **amino acid, and repeat and recycle until you get to the**
11:13:58 **desired, in this case, five amino acid sequence, while still**
11:14:04 **bound to the resin bead and also still having a protecting**
11:14:11 **group on the N-terminus.**

11:14:13 Q. **Now, at this point when you have the peptide sequence**

11:14:17 **that you want attached to the resin bead, what's the next**
11:14:21 **step?**
11:14:21 A. **Well, the next step would be to remove the peptide**
11:14:24 **from the resin bead.**
11:14:25 Q. **And that's shown on DDX-2-27. And if we go to the**
11:14:30 **next slide, what's the result of that cleavage?**
11:14:33 A. **So the result of this cleavage now is you can collect**
11:14:36 **the desired amino acid peptide that you set out to make and**
11:14:42 **it's still bound to the N-terminal protecting group.**
11:14:45 Q. **Now, is this protected peptide the final product in**
11:14:48 **your synthesis?**
11:14:49 A. **No. In our synthesis, the final product would be the**
11:14:53 **five amino acid peptide without the N terminal protecting**
11:14:57 **group.**
11:15:15 Q. **This protected peptide with the N-terminal protecting**
11:15:18 **group on it here, is this an intermediate?**
11:15:22 A. **This would be an intermediate on the pathway to making**
11:15:27 **the five-amino-acid peptide.**
11:15:29 Q. **What would the next step be?**
11:15:32 A. **The next step would be to move the N-terminal**
11:15:36 **protecting group.**
11:15:37 Q. **We will talk about this later. Can you talk about**
11:15:40 **whether this protecting group removal was difficult in 1989?**
11:15:46 A. **No. Removing of the protecting groups that were**
11:15:50 **widely used for peptides synthesis would have been extremely**

11:15:54 **easy to remove at this stage.**

11:15:56 Q. **Let's look at the next slide. It's DDX2-29. What is**

11:16:08 **it showing here?**

11:16:08 A. **This is showing the five-amino-acid peptide with the N**

11:16:11 **protecting group removed, N-terminal protecting group**

11:16:16 **removed.**

11:16:16 Q. **Let's go to the next slide, DDX-2-30. As of 1989 what**

11:16:24 **were the most common protecting groups used to protect the**

11:16:29 **amino terminus of amino acid groups in solid phase**

synthesis?

11:16:31 A. **So there were a wide variety of protecting groups**

11:16:35 **available and useful for this purpose. By far the most**

11:16:38 **widely used ones were referred to here as Boc and Fmoc.**

11:16:43 Q. **Boc and Fmoc, are they acronyms for those long names**

11:16:49 **you have there?**

11:16:50 A. **They are acronyms for these long chemical names.**

11:16:53 Q. **Did either of these N groups have an advantage over**

11:16:57 **the other?**

11:16:57 A. **Yes. Fmoc had an advantage over Boc.**

11:17:01 Q. **Why was that?**

11:17:02 A. **Fmoc was easier to remove than Boc.**

11:17:05 Q. **Let's look at the next slide, which is DDX2-31, can**

11:17:11 **you use this to talk about the advantages of Fmoc please?**

11:17:15 A. **Yes. So it turns out that in the process of making**

11:17:19 **peptides you might also need to protect the side chain**

11:17:22 **functional groups on these amino acids. And this**
11:17:25 **illustrates that here in this picture. Here you have amino**
11:17:30 **acid 1, 3 and 4, with the side chain that has a protecting**
11:17:35 **group on it. And the N terminus have another different**
11:17:39 **protecting group on it.**
11:17:41 Q. **Let's go play the animation. Mr. Chase, here we are**
11:17:47 **looking at Slide DDX2-31.**
11:17:51 **What are you showing there?**
11:17:53 A. **This is showing the N-terminal protecting group, which**
11:17:57 **is Fmoc in this case, it had the advantage that it could be**
11:18:02 **removed without disturbing the blocking groups of the other**
11:18:05 **amino acids or in fact disturbing any of the other chemistry**
11:18:07 **that goes on in peptide synthesis.**
11:18:10 Q. **When was the Fmoc first designed as a protecting group**
11:18:14 **used in organic synthesis?**
11:18:16 A. **It was first designed in the early 1970s.**
11:18:19 Q. **When was Fmoc first used in solid phase peptide**
11:18:24 **synthesis?**
11:18:24 A. **It was first used in solid phase peptide synthesis in**
11:18:27 **the late 1970s.**
11:18:29 Q. **I am going to show you JTX-16, which is an article by**
11:18:33 **Chang, Mr. Chase has put up the cover page of that article.**
11:18:36 **When was the Chang article published, Doctor?**
11:18:39 A. **The Chang article was published in 1978.**
11:18:42 Q. **In layman's terms, what is the subject matter of the**

11:18:46 **Chang article as reflected in the title?**

11:18:48 A. **So the subject matter is to describe the use of the**

11:18:56 **Fmoc group, which is here designated by its chemical name.**

11:18:59 **The use of the Fmoc group in solid phase peptide synthesis.**

11:19:06 Q. **I would like to put up an excerpt from Chang, it is at**

11:19:10 **Page JTX-16.2. What is Chang saying here?**

11:19:15 A. **So here he is saying that you can use the Fmoc group**

11:19:19 **in solid phase peptide synthesis and it has the desirable**

11:19:24 **feature that it can be removed by mild base treatment.**

11:19:28 Q. **Let's put up another excerpt, this Bodanszky reference**

11:19:33 **we looked at earlier which was DTX-187. This is from Page**

11:19:43 **182.0086 and 182.0165. What is Bodanszky saying here about**

11:19:50 **Fmoc?**

11:19:52 A. **Bodanszky is saying basically the introduction of Fmoc**

11:20:01 **in solid phase peptide synthesis was a major step forward in**

11:20:03 **solid phase peptide synthesis, because of the utility, ease**

11:20:05 **and utility with which it could be removed from the**

11:20:09 **N-terminal amino group.**

11:20:12 Q. **I would like to put up DTX-60 in your binder, which is**

11:20:17 **a copy of the Breipohl article. When was the Breipohl**

11:20:23 **article published?**

11:20:23 A. **The Breipohl article was published in 1986.**

11:20:28 Q. **Are any of the authors on the Breipohl article**

11:20:32 **inventors on the '333 patent?**

11:20:35 A. **Yes, they are.**

11:20:36 Q. **Which authors?**

11:20:37 A. **Breipohl and Knolle.**

11:20:42 Q. **Does the Breipohl article discuss solid phase synthesis?**

11:20:47 A. **Yes, it does.**

11:20:48 Q. **In Exhibit DTX60.0003, what is Breipohl saying here in this excerpt?**

11:20:57 A. **Breipohl is stating the advantages of using the Fmoc group in solid phase peptide synthesis. He is specifically saying the Fmoc group avoids the need to repeatedly treat the peptide with harsher chemicals, like acid and liquid hydrogen fluoride.**

11:21:07 Q. **Why would that be an advantage, to avoid acida and liquid hydrogen fluoride?**

11:21:18 A. **It would greatly facilitate the yield and purity of the final product and the ease of making the final product.**

11:21:24 Q. **Now, in addition to Fmoc and Boc, were any other types of amino protecting groups known in the art in 1989?**

11:21:29 A. **Yes, there were a large number of amino protecting groups known in the art.**

11:21:36 Q. **Let's put up an exhibit from DTX-187, which is an excerpt from the Greene book. What is the title of that text?**

11:21:41 A. **The title is Protective Groups in Organic Synthesis.**

11:21:45 Q. **When was the Greene excerpt published?**

11:21:46

11:21:52

11:21:56

11:21:57

11:22:00

11:22:04 A. **I believe it was 1981 -- I am sorry, 1988.**

11:22:16 Q. **Now, were there any differences -- sorry. I skipped a question here. Let's put up Slide DDX-2-35. This is an excerpt from DTX-187 --**

THE COURT: Doctor, I see a copyright of 1981?

THE WITNESS: Yes. I was right.

BY MR. JAMES:

11:22:47 Q. **This table is from Greene. Right?**

11:22:49 A. **Yes, it is.**

11:22:49 Q. **Can you explain what is being shown by Greene in this table?**

11:22:54 A. **This is a list of other possible protecting groups that you could use to protect the amino group.**

11:23:00 Q. **Were there any differences between how a person of skill in the art in 1989 would have viewed these protecting groups as compared to Fmoc and Boc?**

11:23:12 A. **A person of skill in the art would know them to have advantages over all of these groups with respect to ease of removal.**

11:23:22 Q. **But as of 1989 would a person of ordinary skill in the art have known how to remove these groups from a peptide?**

11:23:30 A. **Yes, they would.**

11:23:31 Q. **We touched on bradykinin earlier. What does bradykinin do in the body?**

11:23:38 A. **Bradykinin has several effects on the body. It**

11:23:45 **reduces pain and inflammation. It lowers blood pressure.**
11:23:49 **And third, it induces contraction of smooth muscle.**
11:23:53 Q. **At a very high level, how does the bradykinin peptide**
11:23:57 **trigger those effects?**
11:23:59 A. **Bradykinin triggers those effects as we have already**
11:24:07 **heard by bonding to a molecule that we have referred to as a**
11:24:07 **receptor. When it binds to the receptor, the receptor is**
11:24:10 **like a lock and bradykinin is like a key and bradykinin is**
11:24:15 **able to bind to that lock and actually turn the lock. And**
11:24:19 **that causes a signal to be transmitted.**
11:24:22 Q. **We touched on this earlier as well, but as of 1989 was**
11:24:28 **there work being done on bradykinin analogs?**
11:24:31 A. **Yes, there was.**
11:24:32 Q. **Can you describe generally what was going on in the**
11:24:36 **field of bradykinin analog research in the 1980s?**
11:24:40 A. **Yes, in the 1980s there were large efforts being made**
11:24:44 **to construct modified bradykinin peptides to understand**
11:24:53 **structure/activity relationships of the bradykinin molecule.**
11:24:54 Q. **Were researchers trying to understand bradykinin**
11:24:58 **antagonists?**
11:24:58 A. **Yes, they were trying to make bradykinin antagonists.**
11:25:01 Q. **Can you explain in a general sense what a bradykinin**
11:25:06 **antagonist is?**
11:25:06 A. **A bradykinin antagonist would be a molecule that would**
11:25:09 **bind to that receptor, that we just talked about, the**

11:25:12 **bradykinin receptor on certain kinds of tissues. It would**
11:25:15 **occupy the space that bradykinin would bind to but would not**
11:25:20 **be able to turn that key and lock the way bradykinin would.**
11:25:23 **So it would prevent bradykinin binding to that receptor and**
11:25:29 **transmitting that signal.**
11:25:30 Q. **We talked about a bradykinin antagonist. What would a**
bradykinin agonist be?
11:25:37 A. **A bradykinin agonist would de doing the same thing**
11:25:41 **that bradykinin would be. It would bind to that receptor**
11:25:45 **and turn the lock, transmit the signal.**
11:25:46 Q. **Let's put up the face page of JTX-28. This is a copy**
11:25:57 **of United States Patent 4,693,993. Doctor, when did the**
11:26:01 **'993 issue?**
11:26:03 A. **This patent issued on December 15, 1987.**
11:26:07 Q. **Can you explain what the '993 patent is?**
11:26:10 A. **Yes, the '993 patent is the first disclosure of how to**
11:26:16 **make a modified bradykinin analog that would be a bradykinin**
11:26:21 **antagonist.**
11:26:21 Q. **Who are the inventors on this patent?**
11:26:23 A. **The inventors on this patent are John Stewart and**
11:26:27 **Raymond Vavrek.**
11:26:29 Q. **Can you tell us a little bit about Dr. Stewart's group**
11:26:32 **and his work in the 1980s on bradykinin?**
11:26:39 A. **Yes. Dr Stewart and his group was the most active**
11:26:44 **leading group at the time. They were making all the**

11:26:48 advances, they made the breakthrough of discovery in the
11:26:48 this field. They were making all the advances and making
11:26:51 the breakthrough of how to convert a bradykinin agonist into
11:26:54 an antagonist.
11:26:56 Q. What is the importance of making a bradykinin agonist
11:27:00 into an antagonist?
11:27:01 A. A bradykinin antagonist is very important because it
11:27:05 opens up the doors to studying the biological functions and
11:27:10 mechanism of bradykinin and it allows one to start thinking
11:27:13 about constructing therapeutics to block bradykinin.
11:27:18 Q. Let's put up an excerpt from the '993 patent, this is
11:27:23 from JTX-28.2, the patent, Column 2, Lines 1 through 8. Can
11:27:30 you explain what Dr. Stewart is saying here?
11:27:33 A. Here Stewart is sort of reiterating what I just said.
11:27:36 He is saying the absence of the antagonist up until this
11:27:40 time severely hindered the advance of the field at the time.
11:27:46 That you needed a bradykinin antagonist to open up the doors
11:27:52 for improved understanding of the mechanism and function of
11:27:58 bradykinin.
11:27:58 Q. He mentioned diagnostic use and development of
11:28:03 therapeutic agents. Can you talk about those two things,
11:28:06 please?
11:28:07 A. With an antagonist, what you can do is start off by
11:28:11 asking what are the biological effects that you can
11:28:13 attribute directly to bradykinin in a complex system like

11:28:16 **the body. But then you also can use antagonists to evaluate**
11:28:23 **biological effects in vivo of blocking those signals being**
11:28:31 **transduced by bradykinin and evaluate whether they can be**
11:28:33 **useful therapeutically.**
11:28:34 Q. **Let's put up another excerpts from the '993 patent,**
11:28:39 **this is from Page JTX28.3, Column 3, Lines 12 to 30 from the**
11:28:45 **patent, we have highlighted the first sentence under the**
11:28:49 **Summary of the Invention. Can you explain what Dr. Stewart**
is saying here?
11:28:53 A. **Here he is describing how to make a bradykinin**
11:29:00 **antagonist from the bradykinin itself. The key change, as**
11:29:05 **pointed out here, is to modify the proline ring in the 7**
11:29:09 **position, here he is saying in a unique manner.**
11:29:11 Q. **The next sentence, let's look at that, which we have**
11:29:15 **highlighted on JTX-2-37, what is he saying about the**
11:29:21 **invention specifically?**
11:29:22 A. **Here he is saying what the unique manner is. He is**
11:29:27 **saying the unique manner is to take proline in position 7**
11:29:30 **and replace it with an aromatic amino acid of the D**
11:29:35 **configuration. And that change will make a bradykinin**
11:29:38 **peptide into a bradykinin antagonist.**
11:29:43 Q. **In the last portion of this paragraph, we have**
11:29:45 **highlighted it, what is the doctor saying here about his**
11:29:49 **invention?**
11:29:49 A. **He is saying that you can take in the context of that**

11:29:53 change in the 7 position, where you have now removed the
11:29:56 proline and put in a D aromatic amino acid, that you can now
11:30:01 make other changes to that protein in that context, to that
11:30:05 peptide, and those other changes can add to the efficacy of
11:30:11 the bradykinin antagonist.
11:30:12 Q. He mentioned antagonist potency in that section. What
11:30:18 does that mean?
11:30:18 A. That is one of the ways you can enhance the efficacy.
11:30:21 One way is to enhance the potency. You can enhance the
11:30:24 potency by increasing the affinity with which the molecule
11:30:29 binds to the receptor.
11:30:30 Q. What do you mean by affinity?
11:30:32 A. Affinity is the tendency that it would bind to the
11:30:40 receptor or be released from the receptor. The tightness of
11:30:48 the complex with the receptor.
11:30:49 Q. He also mentioned there on that text on DDX2-37
11:30:55 resistance to enzymatic degradation?
11:30:58 A. Yes. That is also a very important way to enhance the
11:31:02 efficacy of the antagonist. That would enhance the efficacy
11:31:05 by extending the lifetime in vivo by blocking or making the
11:31:12 peptide, the antagonist, resistant to enzymes that would
11:31:17 degrade it. These are the enzymes that we talked about
11:31:20 before that clip peptide bonds.
11:31:23 These are enzymes that cleave these peptide
bonds to degrade the enzyme, and that will limit the

lifetime of this peptide in vivo, and the short half-life in vivo would decrease the efficacy, and the longer half-life would increase the efficacy of the antagonists.

11:31:39

Q. And then lastly he mentioned tissue specificity. Can you talk about what that means?

11:31:39

A. That could also be a desired feature in that you would now be able to target the receptors in certain tissues but leave them alone in other tissues.

11:31:44

Q. I would like to talk now about structure-activity relationships. What is a structure-activity relationship?

11:31:47

A. A structure-activity relationship is a collection of data whose purpose is to understand what parts of the molecule do. What you do is go about making modified peptides and characterize their biological characteristics and a collection of that data would be referred to as a structure-activity relationship.

11:31:50

Q. Why would a researcher generate a structure-activity relationship for a peptide?

11:31:55

A. There are a number of reasons. But the two main reasons are to determine which parts of the bradykinin molecule in this case are responsible for which of its biological activities, for example, which parts of the molecule are crucial for agonist versus antagonist activity, which portions are responsibility for susceptibility to degradation by enzymes and other things like that.

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11:32:57 **It would also be important to serve as guideposts. Once you have that structure-activity relationship, it would tell the person skilled in the art what they might be able to do, and the next objective they may be looking to achieve, whatever that may be. They would have a roadmap. They would say we know we have done this. These are the effects. We might be able to do more and do this.**

11:33:24 Q. **Did Dr. Stewart disclose any structure-activity relationships that he had derived from his work from bradykinin analogs in the 1980s?**

11:33:33 A. **Yes, he did.**

11:33:33 Q. **Were those disclosed in the '993 patent?**

11:33:36 A. **Yes, they are.**

11:33:39 Q. **The next slide, let's look at that, it shows Tables 1 and 2 from the '993 patent, this is from JTX-28.3, the '993 patent, Lines 12 to 59 from that patent. What are those tables showing from a high level?**

11:33:58 A. **From a high level, these two tables summarize Dr. Stewart's structure-activity relationships.**

11:34:06 Q. **Beginning at Table 2, which is called characteristics of bradykinin antagonists, can you explain what Dr. Stewart is saying here, starting with that line of text across the middle?**

11:34:21 A. **The line of text across the middle is the bradykinin**

11:34:25 **sequence.**

11:34:08 Q. **And there are some red numbers. Were those in the**

11:34:11 **original?**

11:34:12 A. **No. These red numbers were not in the original. I**

11:34:14 **added them to make it clear that we were talking about**

11:34:18 **bradykinin and to line it up with the bradykinin sequence**

11:34:20 **that we have already seen.**

11:34:23 Q. **Now, are any of the changes that are identified in**

11:34:25 **Table 2 more important than any of the other changes listed**

11:34:29 **there?**

11:34:29 A. **Yes. You can see that Dr. Stewart said the critical**

11:34:33 **change for antagonist activity is in position 7.**

11:34:36 Q. **And let's look at Table 1 now. Can you briefly**

11:34:44 **describe what is illustrated in Table 1 starting again with**

11:34:49 **that sequence in the middle?**

11:34:51 A. **Right. So here Dr. Stewart lists the number of**

11:34:54 **different substitutions that he made to the proline in**

11:35:00 **position seven, and that all of these substitutions all**

11:35:04 **conferred antagonist activity on the bradykinin molecule.**

11:35:10 Q. **You mentioned that he was indicating substitutions at**

11:35:13 **position seven. How is that shown in Table 1 in the**

11:35:19 **highlighted text?**

11:35:20 A. **Well, here are the three letter amino acid codes**

11:35:28 **that's highlighted in yellow. Each one of these was**

11:35:31 **substituted for proline and that's indicated by this arrow.**

11:35:35 **These groups were each individually tested in this position.**

11:35:40 Q. **And how many different options does he list there?**

11:35:43 A. **Here, he lists eight different options.**

11:35:45 Q. **Are there any common features among the eight options that are listed at the seven position?**

11:35:48

11:35:49 A. **Yes, there are.**

11:35:50 Q. **What are those?**

11:35:51 A. **All of these amino acids are in the D configuration, the unnatural configuration we talked about earlier, and all but one are aromatic D-amino acids.**

11:35:56

11:36:00

11:36:06 Q. **I want to talk just a little bit more about what an aromatic amino acid is or what they are.**

11:36:09

11:36:12 **Let's look at the next slide, which is DDX-2-39. Can you tell us what you're illustrating on this slide?**

11:36:15

11:36:18

11:36:18 A. **So this just illustrates some examples of aromatic amino acids.**

11:36:23

11:36:24 Q. **And starting on the left-hand side, can you explain what makes D-phenylalanine, for example, aromatic?**

11:36:29

11:36:37 A. **We've seen D-thienylalanine. This is the unnatural configuration. Phenylalanine is aromatic because it has the six-membered ring with these double bonds, and this arrangement that might be recognized by most people as a benzene ring, it's this arrangement that confers aromatic character.**

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11:36:57 Q. **And then in the middle, D-thienylalanine. Can you explain the aromaticity of that?**

11:37:03 A. **So this is a non-naturally occurring amino acid. Here you have a five-membered ring, and it is the combination of the five-membered ring and these two double bonds plus this sulfur atom. That structure confers on this side chain.**

11:37:06 11:37:08 11:37:11 11:37:14 11:37:19

11:37:25 Q. **And then finally on the far right you have something labeled D-Pal. Can you explain what you are showing there?**

11:37:28 11:37:31

11:37:31 A. **Yes. So as you can see, D-Pal looks a great deal like D-phenylalanine. They both have a six-membered ring with three double bonds. The difference is that D-Pal has a nitrogen in the ring.**

11:37:35 11:37:41 11:37:45

11:37:47 **MR. JAMES: Your Honor, with your permission, we're going to be referring to those tables again a few times and we'd like to put a board up.**

11:37:47 11:37:49

BY MR. JAMES:

11:38:48 Q. **Can you see that, Dr. Bachovchin?**

11:38:49 A. **Yes, I can see that. Yes.**

11:38:51 Q. **Okay.**

11:38:52 **MS. KUZMICH: Your Honor, excuse me. Permission to move.**

11:38:54 11:38:54 **THE COURT: You can look at it.**

11:38:55 **MS. KUZMICH: Thank you, your Honor.**

11:39:15 **THE COURT: Counsel, would you like to work at this desk here?**

11:39:18 **MS. KUZMICH: That would be great. Thank you. Thank you.**

11:39:20 **THE COURT: We can get you a chair.**

11:39:21 **Doctor, can you see that board?**

11:39:22 **THE WITNESS: Yes.**

11:39:28 **THE COURT: It's an eye test.**

11:39:29 **THE WITNESS: It's an eye test.**

11:39:30 **MR. JAMES: I had originally thought I might put it in the jury box.**

11:39:31 **THE COURT: That's fine. Wherever counsel want it. Most importantly, the witness.**

11:39:33 **MR. JAMES: Thank you.**

11:39:36 **THE COURT: Can you see that?**

11:39:37 **THE WITNESS: Yes.**

11:39:39 **THE COURT: Counsel, can you see?**

11:39:41 **MS. KUZMICH: Thank you. Yes, your Honor.**

11:40:02 **BY MR. JAMES:**

11:40:05 Q. **Dr. Bachovchin, turning back now to DDX-2-39, these three amino acids that you've shown here, and looking now at the tables in the '993 patent, Table 1, are those three amino acids listed for position seven in the '993 patent?**

11:40:05 A. **Yes, they are. So you can see that D-phenylalanine is listed right here. D-Pal is listed here and**

11:40:06

11:40:18

11:40:22

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11:40:48 **D-thienylalanine is listed right there.**

11:40:52 Q. **Now, I'd like to walk through some of the other**

11:40:56 **effects that are listed in Table 2 and starting in the lower**

11:41:00 **left-hand corner, there's a reference to conferring enzyme**

11:41:03 **resistance.**

11:41:04 **Can you talk about what that is saying in Table**

11:41:07 **2?**

11:41:07 A. **Right. So Dr. Stewart's structural activity**

11:41:11 **relationships revealed that he could provide stability or**

11:41:15 **resistance to protease inhibition by making substitutions**

11:41:19 **or, I'm sorry, additions in the zero position, adding**

11:41:23 **something on the N-terminus, and his preferred substitution**

11:41:26 **there was D-Arginine.**

11:41:28 Q. **And then in the upper left-hand corner of Table 2, it**

11:41:36 **says there are changes that confer tissue selectivity. Can**

11:41:39 **you explain that?**

11:41:39 A. **Yes. So he also, the structure activity relationship**

11:41:45 **data indicates that making changes to the two and three**

11:41:49 **positions would confer changes in tissue specificity.**

11:41:52 Q. **And can you just remind us very briefly what that**

11:41:55 **means?**

11:41:55 A. **It means that in would concentrate on certain tissues**

11:42:02 **and avoid others.**

11:42:03 Q. **Now, on the bottom right there is a reference to**

11:42:07 **alterations that enhance potency.**

11:42:09 A. **Yes. Here he is showing that you can modify the five**
11:42:13 **position and six position and the eight position and get**
11:42:17 **enhanced potency of the antagonist that already had the**
11:42:22 **preferred substitution, one of these in position seven.**
11:42:25 Q. **And what was the first substitution that he listed in**
11:42:32 **Table 1 for enhancing potency at the five and eight**
11:42:38 **positions?**
11:42:38 A. **The first one is thienylalanine.**
11:42:41 Q. **Now, just looking back for a moment, Dr. Bachovchin,**
11:42:46 **at position seven, would the person of skill in the art have**
11:42:51 **believed that this is an exhaustive list of the changes that**
11:42:54 **could be made to these molecules?**
11:42:55 A. **No. As I said earlier, this would tell a person of**
11:42:58 **skill in the art what are the attributes of other amino**
11:43:02 **acids that would likely, would have a reasonable expectation**
11:43:06 **would also work. Here you're saying its character is**
11:43:09 **D-amino acid that has hydrophobic character, so that would**
11:43:13 **tell a person of skill in the art that there's other amino**
11:43:16 **acids in the D configuration with hydrophobic character, not**
11:43:21 **yet tested by Dr. Stewart, that would have a reasonable**
11:43:25 **expectation of working in that position.**
11:43:27 Q. **Would that be true of the other lists that he provided**
11:43:29 **in Table 1 as well?**
11:43:30 A. **Yes. Well, yes, it would, not that they're**
11:43:35 **D-aromatic, but what the other character of those amino**

11:43:37 **acids have.**

11:43:38 Q. **I guess my question is: Would a person of skill in**

11:43:41 **the art, would he or she have thought those were exhaustive**

11:43:46 **lists?**

11:43:46 A. **A person of skill in the art would not view these as**

11:43:48 **exhaustive lists of the amino acid substitutions that could**

11:43:51 **work in those positions.**

11:43:52 Q. **Was Dr. Stewart testing his peptides for enzymatic**

11:43:58 **resistance?**

11:43:59 A. **Yes, he was.**

11:44:00 Q. **And was he testing his peptides for their potency?**

11:44:04 A. **Yes, he was.**

11:44:06 Q. **Were the tests for potency and enzymatic resistance,**

11:44:12 **were those already known by others in the field in 1989?**

11:44:14 A. **Yes, they were.**

11:44:16 Q. **Dr. Bachovchin, by 1989 were there any other prior art**

11:44:25 **peptide bradykinin antagonists that would have stood out as**

11:44:28 **particularly effective in the field?**

11:44:29 A. **Yes, there were.**

11:44:30 Q. **And what would those have been?**

11:44:32 A. **Well, one that expressly stood out was the compound**

11:44:35 **referred to often as B-3824.**

11:44:39 Q. **Let's look at the next slide, Mr. Chase. This is**

11:44:44 **DDX-2-41. This is an excerpt from the '993 patent, again.**

11:44:52 **Example 21. Dr. Bachovchin, can you tell us what Example 21**

11:44:56 **is?**

11:44:56 A. **So this is showing the sequence of a molecule referred**
11:44:59 **to in the literature as B-3824. It was also referred to and**
11:45:07 **known in the literature by several other names indicated**
11:45:10 **here.**

11:45:10 **And so the sequence here as you can see,**
11:45:12 **this is a bradykinin analog. This gives the sequence, and**
11:45:14 **this gives the sequence in terms of the modifications of**
11:45:19 **bradykinin.**

11:45:19 **So this is bradykinin with D-Arginine in**
11:45:23 **position zero, hydroxyproline in position three,**
11:45:30 **thienylalanine in positions five and eight, and D-Phe in**
11:45:31 **position 7. So that is the bradykinin analog with those**
11:45:34 **modifications that constitutes B-3824.**

11:45:42 Q. **Let's look at the next slide, DDX-2-42. And starting**
11:45:45 **with the D-Arginine on the left-hand side, can you describe**
11:45:53 **how the sequence of B2834 compares to Dr. Stewart's SAR**
11:45:57 **data?**

11:45:57 A. **Yes. So as you can see, the sequence is quite**
11:46:00 **consistent with Dr. Stewart's SAR data. It actually is like**
11:46:05 **the embodiment of the SAR data. Here, we have substitution**
11:46:09 **at position zero being arginine and that is the preferred**
11:46:14 **substitution that is out of Dr. Stewart's SAR. Here, it has**
11:46:21 **the hydroxyproline, and that is one of the preferred**
11:46:24 **substitutions at position three in Dr. Stewart's SAR.**

11:46:30 **B-3824 hasas the thienylalanine at position**
11:46:33 **five, and that's one of the preferred substitutions of Dr.**
11:46:38 **Stewart, identified them by the SAR at that position. Here**
11:46:41 **we have the crucial D-aromatic at seven, which in this case**
11:46:45 **is D-Phe. That clearly is one of the amino acids in Dr.**
11:46:49 **Stewart's position seven.**
11:46:50 **And, finally, we have in position 8 in**
11:46:53 **B-3824, thienylalanine, and that also was one of the**
11:46:58 **preferred substitutions identified by Dr. Stewart in his**
11:47:01 **structure activity relationship.**
11:47:02 Q. **Let's look at the next slide, which is an excerpt from**
11:47:06 **the '993 patent as well, DDX-2-43. This table is found in**
11:47:13 **column 14, lines 42 to 67 on Page 28.8.**
11:47:18 **Dr. Bachovchin, what information is provided in**
11:47:22 **this table?**
11:47:23 A. **Well, so this table gives a list of bradykinin**
11:47:25 **antagonists. You can see bradykinin is the peptide that's**
11:47:29 **modified, and this describes the modifications, so it lists**
11:47:34 **and compares the structures of these modified bradykinins**
11:47:37 **and it shows how they perform in two biological tests. In**
11:47:42 **this case, this is a rat uterine test and a guinea pig ileum**
11:47:50 **test.**
11:47:50 Q. **You have a highlighted structure there. Can you**
11:47:52 **explain why?**
11:47:53 A. **This highlighted structure is B-3824.**

11:47:56 Q. **And what do the data provided in this table say about B-3824?**

11:48:02 A. **So this number in both of these columns, the column to the left and column to the right, these numbers are referred to as pA2 numbers. And all we need to know about those is that the bigger the number, the more potent the agonist analog is as an antagonist, the more potent the analog is as an antagonist.**

11:48:24 **You can see the B-3824 has the biggest pA2 value of all of the various analogs tested in this table. Its value is 7.2 and no other analog has a greater pA2 value than that.**

11:48:41 Q. **And let's look at DTX-111, which is in your binder. Let's put up the cover of this article. This is the Schachter article.**

11:48:55 **Dr. Bachovchin, when was the Schachter article published?**

11:48:59 A. **The Schachter article was published in 1987.**

11:49:02 Q. **And who were the authors on the Schachter article in addition to Dr. Schachter?**

11:49:07 A. **Well, as you can see, in addition to Dr. Schachter, there's several others, but there's also Dr. Stewart and Dr. Vavrek who were co-authors on this paper. And as I mentioned earlier, they were the major drivers in the full bradykinin antagonist field.**

11:49:25 Q. **Does the Schachter article discuss B-3824?**

11:49:29 A. **Yes, it does.**

11:49:30 Q. **Let's put up an excerpt from Schachter. This is DTX-111, Page 1, and there's a table and some text.**

11:49:40 **Starting with the table, can you explain what information is provided there, Doctor?**

11:49:45 A. **So this table is comparing five different bradykinin antagonist peptides, and it's comparing the sequence of these peptides. And as you can see, it's comparing them to the starting structure bradykinin, and here it's listing the, their potencies as an antagonist peptide. In this case, it's also as an antagonist in this guinea pig ileum test.**

11:50:14 Q. **And how does B-3824 compare to the other BK antagonists there?**

11:50:18 A. **So you can see that, again, in this test it emerges as the most potent of the agonists that it's compared against.**

11:50:27 Q. **And looking at the first sentence in the text that you provided on this slide, what do the authors say there about B-3824?**

11:50:36 A. **So here, the authors are basically stating that they are confirming the earlier paper that we just talked about in which B-3824 emerged as the most potent of the antagonists tested. Here, they are testing it against other**

11:50:56 **agonists against this guinea pig ileum, and it again emerges**
11:51:01 **once more as the most potent of the agonists tested, and**
11:51:04 **they are just saying, they're confirming again that it's the**
11:51:07 **best of the ones they tested.**
11:51:08 Q. **Were they comparing it against agonists or**
11:51:12 **antagonists?**
11:51:12 A. **I'm sorry. Antagonists. They were comparing it**
11:51:15 **against antagonists.**
11:51:16 Q. **I want to turn now and talk about your opinions with**
11:51:19 **respect to obviousness type double patenting. Let's look at**
11:51:25 **the next slide. This is DDX-2-45.**
11:51:30 **Can you explain what's shown on this slide,**
11:51:33 **please?**
11:51:33 A. **Yes. So this shows a face page comparing the two**
11:51:37 **patents at issue here. On the left is the '7,803 patent and**
11:51:41 **on the right is the '333 patent.**
11:51:43 Q. **How does the ownership of these two patents compare?**
11:51:46 A. **Well, as you can see, the ownership is identical.**
11:51:49 Q. **How do the inventors compare?**
11:51:51 A. **Again, as highlighted, you can see there are a number**
11:51:55 **of inventors in common on these two patents.**
11:51:58 Q. **Which of these two patents issued first?**
11:52:01 A. **The '7,803 patent issued on January 28th, 1997. It**
11:52:07 **was the first of these two to be issued.**
11:52:09 Q. **When did the '333 patent issue?**

11:52:11 A. **The '333 patent issued July 15th, 1997.**

11:52:15 Q. **And just for the record, as the slide indicates, the '7,803 patent is DTX-59 and the '333 patent is JTX-1.**

11:52:41 **Let's discuss the asserted claim, claim 14, and if we could put that up, Mr. Chase. Thank you.**

11:52:47 **It begins with the words, "A peptide of the formula." Can you remind us again what a peptide is?**

11:52:54 A. **Yes. So a peptide is a polymer. It's a linear sequence of amino acids linked together by peptide bonds.**

11:53:02 Q. **Is the peptide of claim 14 defined?**

11:53:05 A. **Yes. The peptide of claim 14 is very well designed.**

11:53:09 Q. **How is it defined?**

11:53:10 A. **It is defined by the sequence of the amino acids as defined by the three letter code that represents each of the amino acids that are linked together in that sequence.**

11:53:23 Q. **And how many amino acids are included?**

11:53:26 A. **There are ten amino acids.**

11:53:28 Q. **What does that hydrogen or the H on the left of the sequence signify?**

11:53:33 A. **So as we indicated earlier, that indicates that the amino terminus is unprotected, unblocked in this case.**

11:53:42 Q. **And on the far right-hand side, there's an OH. What does that, what does that indicate?**

11:53:48 A. **So that indicates that in this case, the carboxylate group on the C terminal amino acid is present and uncoupled**

11:53:51

11:53:57 to another amino acid or to any other chemical.
11:54:01 Q. Does the ten amino acid sequence that's set out in
11:54:05 claim 14, does that have another name?
11:54:07 A. That peptide is known as icatibant.
11:54:28 Q. In your opinion, Dr. Bachovchin, is there any
11:54:30 ambiguity in this claim as to the identity of the peptide?
11:54:35 A. No, there is no ambiguity whatsoever.
11:54:38 Q. The last part of the claim refers to a physiologically
11:54:40 tolerable salt of said peptide. Would a person of skill in
11:54:45 the art have understood what that meant?
11:54:47 A. Yes, they would.
11:54:48 Q. What would a person of skill in the art have
11:54:52 understood that to mean?
11:54:53 A. They would understand it to mean that if the salt is
11:54:57 administered to a human it would not cause any adverse
11:55:00 effects.
11:55:00 Q. Were there physiologically tolerable salts known to
11:55:05 humans in the art in 1989?
11:55:08 A. Yes, there were.
11:55:09 Q. Is there any ambiguity in that phrase?
11:55:12 A. None whatsoever.
11:55:12 Q. Would a person of ordinary skill in the art have
11:55:15 understood this claim to require the peptide to have any
particular biological activity?
11:55:18 A. No. A person of skill in the art did not require this

11:55:24 peptide to have any particular specific biological activity.
11:55:28 Q. For the record, the claim is found at JTX-1.24, Page
11:55:36 24, Column 44, Lines 44 to 46 of the '333 patent.
11:55:42 Let's turn to the '7,803 claim. The '7,803
11:55:47 claim is DTX-59. If we look at Slide DDX2-47, which is the
11:55:56 '7,803 patent. Column 20, Lines 22 to 49. Doctor, can you
11:56:02 just generally explain what Claim 1 of the '7,803 patent is
11:56:06 directed to?
11:56:07 A. Yes, Claim 1 of the '7,803 patent is directed towards
11:56:15 a family of peptides that have N-terminal blocking groups on
11:56:20 them.
11:56:20 Q. From the point of view of a peptide chemist, can you
11:56:23 explain at a high level how the claim is laid out?
11:56:26 A. Yes. The claim is, from the standpoint of a peptide
11:56:31 chemist, a peptide chemist would understand that the claims
11:56:34 are laid out such that A through I defines the peptide
11:56:39 portion whereas P to Z define the N-terminal extension part.
11:56:45 Q. Would a person of ordinary skill in the art have
11:56:50 understood the group of peptides that is claimed by Claim 1
11:56:53 of the '7,803 patent?
11:56:55 A. He would.
11:56:55 Q. Is there any ambiguity as to the group of peptides
11:56:58 that is covered by the claim?
11:57:00 A. There is no ambiguity whatsoever.
11:57:01 Q. Does Claim 1 of the '7,803 patent require the peptides

11:57:05 to have any particular biological activity?
11:57:07 A. No, it does not.
11:57:09 Q. Let's look now at the A position, which you mentioned
11:57:17 a moment ago. How many options are provided at the A
11:57:19 position?
11:57:20 A. There are five options at the A position, D- or L-Arg,
11:57:24 D- or L-Lys, or a bond.
11:57:28 Q. What does it mean when it says it could be a bond?
11:57:31 A. When it says it could be a bond, it means that the
11:57:37 group is basically optional, you don't have to have it in
11:57:42 the final peptide.
11:57:43 Q. Let's look at B through I portion of the claim. In B
11:57:47 through I, are there portions where there is only one
11:57:52 option?
11:57:53 A. There is only one option in every portion, except for
11:57:58 G.
11:57:58 Q. How many options are there in G?
11:58:00 A. In G there are three options.
11:58:02 Q. How many total peptides are there in the B through I
11:58:09 section of the claim?
11:58:12 A. B through I defines only three different peptides.
11:58:16 Q. Let's turn back and look at the position G for a
11:58:22 second. Can you explain how that has three possibilities
11:58:26 there?
11:58:27 A. Yes. So the three possibilities here are as I say,

11:58:30 **cis-endo, cis-exo, and trans-octahydroindole-2-carboxylic**
11:58:38 **acid.**
11:58:38 Q. **The first one listed, cis-endo, cis-exo,**
11:58:43 **trans-octahydro -- does it have another name?**
11:58:47 A. **Yes. We have mentioned that, another name is Oic.**
11:58:51 Q. **What are cis-exo and trans-Oic, if you will?**
11:58:57 A. **These three are basically stereoisomers of each other.**
11:59:00 **In this case the stereoisomer is in the side chain, not in**
11:59:06 **the central carbon.**
11:59:07 Q. **Is Oic a natural or man-made amino acid?**
11:59:12 A. **A man-made amino acid.**
11:59:15 Q. **What about Tic, which is listed at the Q position, is**
11:59:20 **that a man-made or amino acid?**
11:59:21 A. **That is also a man-made amino acid.**
11:59:24 Q. **Is that Tic listed in the D or L configuration?**
11:59:27 A. **That Tic is in the D configuration.**
11:59:29 Q. **How do you know that?**
11:59:31 A. **You know that by looking at the generic sequence,**
11:59:34 **where it says Q must be D.**
11:59:42 Q. **Let's look at the A through I section. How many**
11:59:53 **peptides are defined in the A through I section?**
11:59:58 A. **15 different peptides.**
11:59:59 Q. **How did you calculate that?**
12:00:02 A. **You have three options in G, and five options in A.**
12:00:05 **Just mathematically, that makes a total of 15 possibilities.**

12:00:09 Q. **Would a person of skill in the art have expected the**
12:00:12 **peptides that are defined in the A through I portion of this**
12:00:16 **claim to have any particular biological activity?**
12:00:18 A. **A person of skill in the art would examine the**
12:00:21 **peptides defined in A through I, and they have a reasonable**
12:00:27 **expectation that they would be bradykinin antagonists.**
12:00:30 Q. **Would that reasonable expectation have informed the**
12:00:33 **selection of options in the claimed positions?**
12:00:37 A. **Yes.**
12:00:38 Q. **What positions would those be?**
12:00:40 A. **A would be, a person of skill in the art would choose**
12:00:47 **D-Arginine in position A because from the prior art it was**
12:00:52 **well known that D-Arginine was a highly preferred amino acid**
12:00:56 **on the N-terminus of the peptide that was a bradykinin**
12:01:02 **antagonist.**
12:01:02 Q. **Looking at the SAR data that we have up on this board,**
12:01:07 **which is DDX2-A, can you explain what the SAR says about the**
D-Arginine at zero?
12:01:16 A. **Yes, the structure-activity relationship says that**
12:01:20 **submissions at this position confer resistance to enzymes**
12:01:25 **and the preferred substitution there was D-Arg.**
12:01:31 Q. **Let's look at the groups of the N-terminus of Claim 1**
12:01:34 **of the '7,803 patent, the Z and P groups. Looking at the Z**
12:01:43 **groups listed here, what is the first option?**
12:01:47 A. **The first option was Fmoc.**

12:01:48 Q. **Remind us, what was Fmoc used for in the prior art?**

12:01:53 A. **The Fmoc is the blocking or protecting group that was the most widely used protecting group in solid phase peptide synthesis.**

12:02:03 Q. **The other groups listed in the Z position, what are they used for?**

12:02:06 A. **Those are also used to protect amino acid groups.**

12:02:06 Q. **Did we talk about those earlier today?**

12:02:10 A. **We talked about blocking groups of this type, yes.**

12:02:13 Q. **Which reference was that that we referred to in that regard?**

12:02:19 A. **That was the Greene reference.**

12:02:25 Q. **Let's look at the next position which is the P position. Can you explain what is listed in the P position?**

12:02:27 A. **The first option in the P position, it can be a direct linkage.**

12:02:30 Q. **What does direct linkage mean?**

12:02:34 A. **P is optional, Z can be directly connected to A.**

12:02:37 Q. **We looked earlier at the A position where it said bond. Is there any difference between direct linkage and bond?**

12:02:37 A. **Not to my understanding, no.**

12:02:40 Q. **The other groups listed in the P position, what are they useful for?**

12:02:43 A. **Those are useful as spacer linkers because those are**

12:02:47

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12:03:03 **amino acids that can be coupled in much the same way as a**
12:03:07 **normal amino acid, but the first several there have a bigger**
12:03:12 **distance between the amino group and the carboxylate group,**
12:03:17 **except for Oic, which has the normal distance between the**
12:03:21 **amino group and the carboxylate group but it is an unnatural**
12:03:27 **amino acid.**
12:03:27 Q. **What would the significance of the direct linkage**
12:03:30 **option in the P position have been to a person of ordinary**
12:03:34 **skill in the art with respect to the other groups that are**
12:03:37 **listed there?**
12:03:38 A. **Well, a person of skill in the art would understand**
12:03:42 **that to mean that P is optional.**
12:03:45 Q. **Could you explain that a little further?**
12:03:47 A. **It means P is not required. You can directly link Z**
12:03:54 **to the A.**
12:03:55 Q. **Does anything in the prior art suggest that putting**
12:03:59 **any of these groups in the P position would be superior to**
12:04:04 **the direct linkage?**
12:04:05 A. **There is nothing in the prior art that would indicate**
12:04:07 **that any of groups listed under P would provide superior**
12:04:11 **properties.**
12:04:11 Q. **Looking at the claim as a whole, about how many total**
12:04:15 **compounds are covered by the '7,803 patent, Claim 1?**
12:04:20 A. **Total number of peptides, around 1100.**
12:04:22 Q. **Would a person of ordinary skill in the art be able to**

12:04:25 **write them all out?**

12:04:26 A. **Yes, he would.**

12:04:27 Q. **Would that be a difficult task?**

12:04:29 A. **It would not be difficult. It might be labor**

12:04:34 **intensive, but not difficult.**

12:04:38 Q. **Looking at the next slide, DDX2-54, if you just select**

12:04:44 **the first option for each of these, what is the resulting**

12:04:48 **peptide?**

12:04:51 A. **So that peptide is basically Fmoc-icatibant.**

12:05:01 Q. **Let's look at the next slide, where we put up**

12:05:08 **Fmoc-icatibant. Is that what we were just discussing, which**

12:05:15 **was the first option for the positions in Claim 1 of the**

12:05:17 **'7,803 patent?**

12:05:18 A. **Yes.**

12:05:19 Q. **What is the second line?**

12:05:22 A. **The second line is Claim 14 of the '333 patent.**

12:05:26 Q. **How do these two peptides compare to one another?**

12:05:31 A. **As you can see, the sequences, starting from the**

12:05:35 **N-terminus to the C-terminus, as illustrated by the three**

12:05:39 **letter codes in these colored balls, the sequence from the**

12:05:43 **N-terminus to the C-terminus, each one is exactly identical.**

12:05:49 **The only difference is the presence of the Fmoc group on the**

12:05:54 **N-terminus of Claim 1 in the '7,803 patent.**

12:06:00 Q. **What would the person of ordinary skill in the art**

12:06:03 **have been motivated to do with that Fmoc?**

12:06:06 A. **A person of ordinary skill in the art would have been**
12:06:10 **motivated to remove the Fmoc.**
12:06:11 Q. **Why would that be?**
12:06:13 A. **Because the person of ordinary skill would recognize**
12:06:15 **that the Fmoc is a widely used entity used to block**
12:06:19 **N-terminus of peptides and it is designed to do that because**
12:06:23 **it is easily removable and, we said earlier, it exists for**
12:06:28 **the purpose of being removed.**
12:06:29 Q. **What would be the result of removing the Fmoc from the**
12:06:34 **peptide of Claim 1 of the '7,803 patent?**
12:06:37 A. **The result of removing the Fmoc group would be the**
12:06:40 **same identical peptide as Claim 14 of the '333 patent.**
12:06:44 Q. **Would a person of ordinary skill in the art have known**
12:06:48 **how to remove the Fmoc from this peptide?**
12:06:51 A. **Yes, he would.**
12:06:53 Q. **Let's look at the next slide, which is DDX2-56. This**
12:06:58 **is an excerpt from the Chang article we looked at earlier.**
12:07:02 **DTX-16.2, please. Looking at the first line, it starts with**
12:07:08 **Fmoc, can you explain what that is?**
12:07:11 A. **Yes. This is a peptide here, in this case the**
12:07:16 **underlying peptide is the dihydrosomatostatin. It is a**
12:07:22 **different peptide. Again, it shows it was made as the Fmoc**
12:07:26 **variant. The Fmoc is on the N-terminus that goes from the**
synthesis of these peptides.
12:07:32 Q. **What is the arrow in the middle pointing down?**

12:07:35 A. **The arrow is pointing that these procedures are to be**
12:07:39 **carried out on this peptide.**
12:07:40 Q. **The step you have highlighted, what is that?**
12:07:43 A. **This is the step that removed the Fmoc group. This is**
12:07:47 **the addition of 50 percent piperidine and dimethylformamide,**
12:07:54 **that mild base, that is a very mild treatment, and results**
12:07:54 **in knocking off the Fmoc group from the piperidine side.**
12:07:57 Q. **What is the bottom sequence you are depicting there?**
12:08:01 A. **That now shows the dihydrosomatostatin peptide now**
12:08:07 **with the Fmoc having been removed.**
12:08:10 Q. **Let's look at DTX-2-57. What are you depicting here?**
12:08:16 A. **Again, this illustrates the Fmoc-icatibant relative to**
12:08:21 **icatibant.**
12:08:23 Q. **What does the reaction arrow indicate?**
12:08:25 A. **The reaction arrow indicates that we are applying the**
12:08:33 **same process of adding piperidine to the Fmoc-icatibant.**
12:08:39 Q. **What are you showing on the bottom line?**
12:08:42 A. **It shows doing that to the peptide would remove that**
12:08:47 **from the Fmoc terminus.**
12:08:48 Q. **How widely known was this process of removing Fmoc by**
12:08:54 **January 1989?**
12:08:55 A. **By January 1989 it was extremely widely known.**
12:08:58 Q. **How does that impact your opinions about the**
12:09:01 **difference between Fmoc-icatibant and icatibant in this**
12:09:04 **case?**

12:09:05 A. **It impacts my opinion that this difference is really a**
12:09:11 **trivial difference, of no real significance.**
12:09:14 Q. **I would like to turn to expectation of success. You**
12:09:19 **understand that plaintiffs' expert, Dr. Walensky, argued**
12:09:23 **that a person of ordinary skill in the art would not**
12:09:26 **recognize any peptides of Claim 1 of the '7,803 patent as**
12:09:34 **viable bradykinin antagonists if the Fmoc were removed?**
12:09:37 A. **Yes, I understand that is his opinion.**
12:09:39 Q. **Do you agree with that?**
12:09:41 A. **No, I do not.**
12:09:42 Q. **Have you summarized the basis of your disagreement**
12:09:45 **with Dr. Walensky?**
12:09:47 A. **Yes, I have.**
12:09:48 Q. **Let's look at DDX2-58. Summarize your opinions in**
12:09:54 **this regard, if you would?**
12:09:55 A. **My opinion is that a person of ordinary skill in the**
12:09:59 **art would know or have a reasonable expectation that the**
12:10:04 **peptide side of Claim 1 of the '7,803 patent would be a**
12:10:10 **bradykinin antagonist based on two things, one, the**
12:10:14 **structure-activity relationships of Dr. Stewart, which**
12:10:18 **indicated that this peptide was a bradykinin analog that**
12:10:24 **incorporated the attributes that Dr. Stewart's structure-**
12:10:29 **activity relationships indicated would be needed or required**
12:10:33 **to produce a bradykinin antagonist, and also by the sequence**
12:10:39 **of the peptide we talked about before from the prior art,**

12:10:43 **B-3824, which was a well known prior art bradykinin**
12:10:49 **antagonist, which was extremely similar in sequence and**
12:10:52 **structure to Claim 1 of the '7,803 patent.**
12:10:56 Q. **Let's talk about the first reason that you mentioned**
12:10:59 **relating to the SAR data. Which SAR data were you referring**
12:11:05 **to?**
12:11:05 A. **The Stewart SAR data as published in the '993 patent.**
12:11:11 Q. **Is that the data that is depicted on that board?**
12:11:17 A. **Yes, it is.**
12:11:18 Q. **Have you prepared a slide that illustrates the options**
12:11:21 **at each position of Claim 1 of the '7,803 patent?**
12:11:27 A. **Yes.**
12:11:27 Q. **The next slide, you have groups listed in the minus**
12:11:32 **two and minus one positions. Can you explain that?**
12:11:36 A. **Yes. These are the options in the '7,803 patent Claim**
12:11:41 **1 patent for the Z position and the P position, here we will**
12:11:46 **read them, minus 1 and minus 2, for clarity of discussion.**
12:11:50 Q. **Does that maintain the reference to the original**
12:11:53 **bradykinin sequence?**
12:11:54 A. **That maintains the reference to the original**
12:11:57 **bradykinin sequence.**
12:11:58 Q. **Without the Z and P groups, how would a person of**
12:12:02 **ordinary skill in the art interpret the structure that would**
12:12:06 **be left over?**
12:12:07 A. **Yes, a person of ordinary skill in the art would look**

12:12:10 at the structure that is left over and would have the
12:12:13 reasonable expectation that that structure would be a
12:12:17 bradykinin antagonist.
12:12:18 Q. Let's talk about the sequence a little bit further.
12:12:21 Let's look at DDX2-60. What positions would a person of
12:12:31 ordinary skill in the art have focused on with respect to
12:12:35 determining whether or not the sequence would be a
12:12:38 bradykinin antagonist?
12:12:39 A. He would focus on these three positions, positions 0,
12:12:43 5 and 7.
12:12:44 Q. Let's start on the left-hand side, at zero, you
12:12:50 circled D-Arginine in Slide DX2-61, was D-Arginine suggested
12:12:58 by Dr. Stewart's structure-activity relationship data?
12:13:01 A. Yes, it was. As you can see looking at Table 1 of Dr.
12:13:06 Stewart's structure-activity relationships, at the zero
12:13:10 position, the preferred position there is an Arginine.
12:13:13 Q. What would the effect of the D-Arg be at zero?
12:13:17 A. As Table 2 indicates, that addition would confer
12:13:20 resistance to enzymes.
12:13:21 Q. How would it do that?
12:13:24 A. It would do that because it's an unnatural amino acid.
12:13:32 An unnatural amino acid on the N-terminus would be resistant
12:13:35 to aminopeptidase degradation, because aminopeptidase would
12:13:37 be looking for amino acids of the L configuration, not of
12:13:39 the D configuration.

12:13:42 Q. **Turning to the next slide, which is DDX2-62, there is**
12:13:47 **a Thi at the 5 position that you circled. Was that**
12:13:51 **suggested by Dr. Stewart's structure-activity relationship**
12:13:55 **data?**
12:13:56 A. **Yes, it was.**
12:13:38 Q. **Can you point that out?**
12:13:41 A. **So if you go to Table 1 of the SAR by Dr. Stewart, you**
12:13:46 **can see the thienylalanine here was the first substitution**
12:13:53 **among the preferred choices of this position.**
12:13:55 Q. **And what does Table 2 say about the effect of that**
12:13:58 **substitution?**
12:13:59 A. **So Table 2 says this would alter, the substitutions in**
12:14:04 **this position, the ones that are listed here, would enhance**
12:14:08 **potency.**
12:14:09 Q. **And looking at the next slide, DDX-2-63, you have a**
12:14:14 **circle around the seven position. What amino acid is**
12:14:18 **disclosed there?**
12:14:19 A. **That amino acid is D-Tic.**
12:14:25 Q. **Now, first, what does the Stewart Table 2 say about**
12:14:30 **the effect of substitutions at the seven position?**
12:14:33 A. **So as we already mentioned, Dr. Stewart has indicated**
12:14:38 **that the attributes that are required for substitution at**
12:14:44 **position seven to have a bradykinin antagonist would be**
12:14:48 **D-amino acid, preferably an aromatic D-amino acid.**
12:14:52 Q. **And what type of amino acid is D-Tic?**

12:14:56 A. **Well, D-Tic is a D-amino acid and it is an aromatic D-amino acid.**

12:15:01 Q. **Was D-Tic known in the prior art?**

12:15:09 A. **D-Tic was known in the prior art.**

12:15:11 Q. **Let's put up DTX-57. This is a copy of U.S. Patent 4,515,803.**

12:15:13 **And when was the '5,803 patent issued, Dr. Bachovchin?**

12:15:25 A. **This patent was issued on May 7, 1985.**

12:15:28 Q. **And let's put up the next slide, DDX-2-64.**

12:15:28 **Does the '5,803 patent disclose what we've been talking about as Tic?**

12:15:31 A. **Yes, it does.**

12:15:37 Q. **Can you explain that from the text that is on the slide, DDX-2-64?**

12:15:41 A. **Here it says that Tic is tetrahydroisoquinoline carboxylic acid. It's saying that Tic and substituted derivatives are readily accessible. It tells you a paper that shows how that can be made. That paper is referenced here. It's a reference that goes all the way back to 1948. So Tic was known for a long time.**

12:15:43 Q. **Let's look at the next slide, which is DDX-2-65. And starting with the blue box in the middle, Dr. Bachovchin, can you explain what you're showing on this slide?**

12:15:46 A. **Well, so the box in the middle shows the structure now**

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12:16:26 of D-Tic.
12:16:27 Q. Okay. And then what is shown in the squares around
12:16:32 D-Tic?
12:16:33 A. So what you see in the circles around D-Tic for
12:16:36 comparison are the structures of the amino acid
12:16:40 substitutions that Dr. Stewart lists here in Table 2 as
12:16:44 substitutions that confer bradykinin antagonist activity
12:16:50 when substituted in position seven.
12:16:52 Q. And by here, just for the record, you were referring
12:16:56 to --
12:16:57 A. Position seven.
12:16:58 Q. -- Table 1 of the '993 patent?
12:17:00 A. Yes. Table 1 of the '993 patent.
12:17:02 Q. Now, how do the structures of the amino acids listed
12:17:07 in the SAR by Dr. Stewart compare to the structure of D-Tic?
12:17:13 A. Well, first of all, they're all D-amino acids.
12:17:16 Second of all, seven of the eight are
12:17:22 aromatic as D-Tic is. If you look closely at D-Tic, you can
12:17:25 see it's very closely similar in structure to all of these
12:17:28 amino acids, and perhaps especially to D-Phe but not that
12:17:34 far different from D-Pal or D-tyrosine or
12:17:42 D-O-methyltyrosine.
12:17:42 Q. And what would a person of ordinary skill in the art
12:17:47 conclude about the likely activity of a bradykinin analog
12:17:50 with D-Tic at position seven based on this information?

12:17:55 A. **Based on this information, a person of ordinary skill in the art would have a reasonable expectation that substituting a D-Tic into position seven of a bradykinin analog peptide would maintain the antagonist activity of that peptide.**

12:18:11 Q. **Let's turn to the next slide. Now, based on the information you've been discussing with respect to the five and 7 positions, can you summarize a person of ordinary skill in the art's understanding regarding the expected activity of the peptides of Claim 1 of the '7,803 patent if the Z and P groups were removed?**

12:18:35 A. **Yes. Well, a person skill in the art would recognize that if you remove the Z and P groups, the peptide that was left would be an analog of bradykinin and it would be an analog of bradykinin that incorporated the key substituents that Dr. Stewart's structure activity relationships taught were needed or required or desired in a bradykinin -- to make a bradykinin antagonist peptide. So a person of skill in the art would have a reasonable expectation that this remaining peptide would be a bradykinin antagonist.**

12:19:13 Q. **Now I want to talk about the second reason you listed on your summary slide. If we could just go back to that, which is DDX-2-67.**

12:19:23 **Can you remind us what your second reason was for your expectation?**

12:19:28 A. **Yes. So a second reason is that a person of skill in**
12:19:32 **the art would look at the sequence of B-3824 and comparing**
12:19:38 **that to the peptide that is left after removing Z and P**
12:19:43 **group from the Claim 1 of the '7,803 patent. That**
12:19:47 **comparison would indicate to a person of skill in the art**
12:19:50 **that the remaining peptide would have, would have a**
12:19:55 **reasonable expectation to have bradykinin antagonist**
12:19:58 **activity.**
12:19:59 Q. **Let's look at the next slide, DDX-2-68. What are you**
12:20:05 **depicting here?**
12:20:06 A. **So this compares the peptide sequence of the prior art**
12:20:11 **compound B-3824 to the sequence of the remaining peptide of**
12:20:16 **Claim 1 of the '7,803 patent.**
12:20:19 Q. **Dr. Bachovchin, what are the similarities between the**
12:20:22 **sequence of B-3824 and the sequence of Claim 1 of the '7,803**
12:20:28 **patent?**
12:20:28 A. **So the similarities are, they're both ten amino acid**
12:20:32 **peptides and they are identical in eight of the ten**
12:20:35 **positions.**
12:20:37 Q. **And what are the differences between these two**
12:20:41 **sequences?**
12:20:42 A. **They exhibit some differences only in position 7 and**
12:20:45 **8.**
12:20:46 Q. **If we could look at that. That's shown on slide**
12:20:48 **DDX-2-68.**

12:20:52 **Let's talk about those two positions. Let's**
12:20:55 **first talk about D-Tic. What amino acid in B-3824 is being**
12:21:00 **replaced with D-Tic?**
12:21:02 A. **So in position 7 of 3824, D-Phe is there and we'll go**
12:21:10 **from that to Claim of the '7803 patent. We're replacing**
12:21:15 **D-Phe with the D-Tic.**
12:21:17 Q. **Did the prior art compare D-Phe and D-Tic?**
12:21:22 A. **Yes.**
12:21:22 Q. **Let's look at DTX-70, please. This is an article by**
12:21:27 **Kazmierski. When did this article publish? We'll put that**
12:21:30 **up on the screen.**
12:21:37 A. **This article published --**
12:21:39 Q. **On the screen in front of you, Doctor.**
12:21:42 A. **1988.**
12:21:43 Q. **And does this article discuss the use of D-Tic?**
12:21:46 A. **Yes, it does.**
12:21:47 Q. **Does this article discuss the use of D-Tic in the**
12:21:50 **context of bradykinin antagonists?**
12:21:52 A. **No, it does not.**
12:21:53 Q. **Would that matter to a person of skill in the art?**
12:21:55 A. **That would not matter to a person of skill in the**
12:21:57 **art.**
12:21:58 Q. **Can you explain why not?**
12:21:59 A. **Well, it does not matter for the purpose of comparing**
12:22:04 **the attributes of the two amino acids with each other.**

12:22:07 Q. **Let's put up an excerpt from Kazmierski. This is DTX-70, pages 4 and 5. Let's start with the structures at the bottom of your slide, DTX-2-69.**

12:22:19 **Can you tell us what is shown there?**

12:22:21 A. **So the bottom of the slide here shows and compares the structure D-Phe and the structure D-Tic.**

12:22:29 Q. **And how do they compare?**

12:22:31 A. **So as you can see, they're very similar. The only differences highlighted here were circled in red. Basically, the side chain aromatic ring is connected to the backbone of D-Tic where it's not connected to the backbone in D-Phe.**

12:22:47 Q. **And what are they saying in the highlighted text?**

12:22:50 A. **So if you can read the highlighted text, it's basically saying that D-Tic can be viewed as a D-Phe. Tic can be viewed as a Phe in which rotation about these is limited.**

12:23:08 Q. **Let's look at the next slide, DTX-2-70. And focusing on that seven position for now, what would the expectation of a person of ordinary skill in the art be with the claimed activity of the '7803 patent be with respect to that D-tic at seven?**

12:23:32 A. **A person of skill in the art would expect substituting the D-Phe for D-Tic would maintain the antagonist activity of B-3824.**

12:23:43 Q. **I'm sorry. So you're substituting the D-Tic for the**
12:23:47 **D-Phe. Is that what you meant to say?**
12:23:49 A. **Yes. Substituting D-Tic for D-Phe would maintain**
12:23:54 **antagonist activity.**
12:23:55 Q. **Now let's look at the Oic at eight, at the eight**
12:23:59 **position.**
12:24:02 **Now, what amino acid -- let me strike that**
12:24:06 **question. I apologize.**
12:24:08 **Was Oic known in the prior art?**
12:24:11 A. **Yes, it was.**
12:24:14 Q. **And if you could turn to DTX-58 in your binder, this**
12:24:20 **is a copy of the Blankley article. My apologies.**
12:24:36 **When was the Blankley article published?**
12:24:38 A. **1987.**
12:24:39 Q. **Does Blankley discuss Oic?**
12:24:41 A. **Yes, he does.**
12:24:42 Q. **Let's put up the excerpt from Blankley here. And this**
12:24:51 **is from DTX-58 at Page one.**
12:24:55 **What is Blankley saying about Oic in this**
12:24:59 **passage?**
12:24:59 A. **So in this passage, Blankley is saying that Oic can**
12:25:05 **substitute or replace proline in a peptide.**
12:25:10 Q. **Okay. Is Blankley discussing Oic in the context of**
12:25:14 **bradykinin antagonists?**
12:25:16 A. **No, he is not.**

12:25:17 Q. **And would that matter?**

12:25:18 A. **It would not matter to a person of skill in the art**

12:25:20 **for this purpose.**

12:25:21 Q. **Now, you mentioned that he was talking about proline.**

12:25:25 **Was there anything in the prior art that suggested proline**

12:25:28 **at position eight of a bradykinin antagonist?**

12:25:31 A. **Yes, there was.**

12:25:32 Q. **Let's look at JTX-38. It's in your binder. It's a**

12:25:37 **copy of U.S. Patent 4,923,963. We have it up on the screen.**

12:25:44 **When was the '963 patent application filed?**

12:25:47 A. **This application was filed on September 2nd, 1987.**

12:25:55 Q. **And who are the inventors?**

12:25:57 A. **The inventors are Stewart and Vavrek.**

12:26:02 Q. **And who is this patent assigned to?**

12:26:08 A. **The patent is assigned to Nova.**

12:26:14 Q. **I'm going to put up an excerpt from the '963 patent.**

12:26:17 **This is from JTX-38, Page 3. It's Column 3, lines 66 to**

12:26:24 **column, I'm sorry, to 67 and Column 4 at lines 44 to 48.**

12:26:30 **And looking at this slide, DTX-2-73, what is the**

12:26:35 **sequence that's depicted in the middle of your slide,**

12:26:37 **Doctor?**

12:26:38 A. **So this is basically illustrating the sequence of a**

12:26:42 **peptide. In fact, in this case, it's the bradykinin**

12:26:46 **peptide.**

12:26:46 Q. **And is the numbering that's provided below those**

12:26:52 letters, is that consistent with the numbering we've been
12:26:56 discussing?
12:26:56 A. The numbering is consistent with the numbering we've
12:27:00 been discussing with respect to bradykinin.
12:27:01 Q. And here, there's a Z listed at the eight position.
12:27:07 Is that the same eight position we've been discussing?
12:27:10 A. That is the same eight position we've been discussing,
12:27:13 yes.
12:27:13 Q. And what does this '963 patent say about the
12:27:16 substitutions that could be made at the Z position in the
12:27:20 highlighted text?
12:27:21 A. So this says that you could substitute D- or L-proline
12:27:27 into the Z position.
12:27:29 Q. Now, let's look back at the SAR data of Dr. Stewart,
12:27:36 Tables 1 and 2 of the '993 patent. That's on the board,
12:27:42 DDX-2A.
12:27:42 Can you explain what those tables disclose at
12:27:45 the eight position?
12:27:46 A. So we're looking at Table 1 of the '993 patent. This
12:27:52 discloses in the eight position that you can have Z six
12:28:00 different substituents put into this position and maintain
12:28:04 bradykinin antagonist activity.
12:28:08 Q. Thank you.
12:28:08 And let's turn to DTX-114 in your binder. This
12:28:13 is the Spragg article. When was the Spragg article

12:28:17 **published, Dr. Bachovchin?**

12:28:19 A. **So the Spragg article was published in 1988.**

12:28:23 Q. **And who are the authors on this article?**

12:28:25 A. **Again, the authors are Spragg, but, again, Raymond Vavrek and John Stewart.**

12:28:30 Q. **And I'm going to put up an excerpt from Spragg. This is from DTX-114, Page 7.**

12:28:38 **Looking at this slide, DDX-2-74, what's shown in Table 1 at the top of the slide?**

12:28:46 A. **So what's shown in Table 1 is a sequence, peptide sequence, again, a bradykinin peptide sequence. Yes, bradykinin sequence.**

12:28:59 Q. **All right. And then there are some red numbers and a red box. Were those in the original?**

12:29:05 A. **No. I added the red box and the red numbers.**

12:29:09 Q. **All right. What's being compared in this table?**

12:29:11 A. **So what's being compared here is the sequence of several bradykinin analogs and bradykinin analogs that are antagonists together with bradykinin itself.**

12:29:27 Q. **And here, the eight position is labeled P2; is that right?**

12:29:32 A. **In this case, the P2 position corresponds in our nomenclature to the eight position.**

12:29:39 Q. **And what does the text just below the table say about the substitutions that could be made at the P2 position?**

12:29:47 A. **This says that the P2 position, you can substitute**
12:29:50 **bulky analogs such as cyclohexylalanine.**
12:29:55 Q. **And what's a bulky analog?**
12:29:58 A. **A bulky analog is basically a big, it's an amino acid**
12:30:03 **with a big side chain.**
12:30:04 Q. **And then at the end of that sentence, it says that, it**
12:30:07 **indicates that minimal steric restraints are observed at**
12:30:10 **this position. What does that mean?**
12:30:11 A. **So that basically means that you can put big groups in**
12:30:15 **that position and not get adverse effects of blocking the**
12:30:22 **desired effects. That it will tolerate large groupings in**
12:30:25 **that position, large side chains in that position.**
12:30:30 Q. **Let's look at the next slide, which is DDX-2-75. And**
12:30:34 **starting with the blue box on the right, Dr. Bachovchin, can**
12:30:37 **you explain what you are showing here?**
12:30:39 A. **So the blue box on the right shows the structure of**
12:30:42 **Oic.**
12:30:43 Q. **And what are the other ten things shown on the**
12:30:49 **right-hand slide?**
12:30:51 A. **So the other ten things are things known to work when**
12:30:54 **put in position eight.**
12:30:55 Q. **Those are all amino acids?**
12:30:56 A. **Those are all amino acids.**
12:30:58 Q. **And Number 10, is that the cyclohexylalanine that was**
12:31:03 **referred to in Spragg?**

12:31:04 A. **Yes. This is the structure cyclohexylalanine that we**
12:31:08 **just talked about in Spragg that can be substituted as well**
12:31:11 **in that position.**
12:31:11 Q. **And for the record, the citations provided here are**
12:31:14 **the '963 patent, Column 3, lines 66 to 67; Column 4, line 45**
12:31:23 **to 4; the '993 patent, column four to line 17 to 57, and**
12:31:29 **then the Spragg article at Page 7.**
12:31:32 **Now, how do these substitutions compare to the**
12:31:36 **structure of Oic?**
12:31:37 A. **So as you can see, they're all structurally very**
12:31:41 **similar. They have attributes of Oic, especially**
12:31:46 **cyclohexylalanine. You can look at cyclohexylalanine, and**
12:31:50 **if you moved it over and superimposed it on Oic, you would**
12:31:55 **see it would line up pretty well everywhere and the only**
12:31:58 **difference here would be the bond between the NH and the**
12:32:01 **cyclohexyl ring. If you connect this with this, you have**
12:32:05 **Oic.**
12:32:05 Q. **And what inference would a person of ordinary skill in**
12:32:08 **the art draw from this information with respect to the**
12:32:10 **inclusion of Oic at the eight position of the '7,803 patent?**
12:32:14 A. **A person of ordinary skill in the art would have a**
12:32:18 **reasonable expectation that if cyclohexylalanine works in**
12:32:23 **that position, Oic would also work.**
12:32:24 Q. **Let's look at the next slide, DDX-2-76. And based on**
12:32:39 **the information that we've just been reviewing, Dr.**

12:32:42 **Bachovchin, how would a person of ordinary skill in the**
12:32:44 **art have viewed the substitutions of D-Tic and Oic in the**
12:32:50 **'7,803 compound as compared to the substitutions found in**
12:32:53 **B-3824?**
12:32:54 A. **Yes. Well, a person of skill in the would recognize**
12:32:59 **these substitutions as what we refer to as conservative**
12:33:02 **substitutions. In other words, they're very chemically**
12:33:06 **similar and a person of skill in the art would expect them,**
12:33:09 **would expect that if these work in these positions, that**
12:33:14 **these would also work in those positions.**
12:33:16 Q. **I think I may have skipped one question earlier. So**
12:33:22 **if we could just go back, Mr. Chase, to DDX-2-75 for a**
12:33:30 **moment.**
12:33:30 **Dr. Bachovchin, can you just discuss the compare**
12:33:34 **comparison of Oic and the proline residue listed as number**
12:33:37 **nine?**
12:33:37 A. **Yes. You can see that proline is a five-membered**
12:33:40 **ring, but Oic also has that proline five membered ring. In**
12:33:46 **addition to that, it has a six-membered cyclohexane ring on**
12:33:52 **top of the proline ring. So you can almost view Oic as a**
12:33:56 **combination of proline with cyclohexylalanine and that, it**
12:34:03 **would also tend to support the idea that Oic would be a**
12:34:08 **group that you could substitute in this position based on**
12:34:11 **these structure-activity relationships to expect it to**
12:34:15 **maintain antagonist activity.**

12:34:13 Q. **Let's go to Slide DDX2-77. Here, we are showing B-3824 at the bottom of the slide again. On the basis of the structure of B-3824, and the prior art, how would a person of ordinary skill in the art view the Z and P groups of the '7,803 patent compound?**

12:35:03 A. **Yes, a person of skill in the art, based on the prior art compounds, including B-3824, would now view the Z and P positions as optional and not required or needed for antagonistic activity.**

12:35:19 Q. **Can you just remind us again, if you took off the Z and P groups of Claim 1 of the '7,803 patent compound, how many peptides are defined from A to I?**

12:35:32 A. **As we already mentioned, that would be a total of 15 peptides.**

12:35:38 Q. **You understand that Dr. Walensky has argued that a person of ordinary skill in the art would not have been motivated to remove the Z and P groups because they are listed as part of a final claimed product of Claim 1 of the '7,803 patent?**

12:35:54 A. **Yes, I understand that is his opinion.**

12:35:56 Q. **Do you agree with that?**

12:35:57 A. **No, I do not.**

12:35:59 Q. **Would it change your opinion if it was understood to be a final product?**

12:36:03 A. **No, it would not.**

12:36:03 Q. **Can you explain why not?**

12:36:05 A. **Because it doesn't change my view that it would be an obvious variant of the key underlying peptide structure, and that the person of skill in the art would recognize that the key structure is within the peptide sequence and that the Z position and the P position are not contributing in a significant way and a person of skill in the art would want to remove anything that doesn't have evidence of contributing in a significant way so that they have the smallest molecule that provides the activities that they are looking for.**

12:36:50 Q. **You understand that Dr. Walensky's position is that a person of skill in the art would believe that some of the N-terminal modifications that are listed here in the '7,803 claim might be there to improve solubility and improve enzymatic resistance?**

12:37:08 A. **Yes, I understand that's his opinion.**

12:37:10 Q. **Let's talk about improving solubility. Would a person of skill in the art have perceived any need for the Z or P group here to achieve that purpose?**

12:37:21 A. **No. A person of skill in the art would recognize that the prior art compounds had no problems with solubility so there would be no need to add N-terminal protecting groups to improve solubility.**

12:37:34 Q. **Let's talk about adding enzymatic resistance. Would a**

12:37:38 person of skill in the art have observed any need for the Z
12:37:41 or the P groups to achieve that purpose?
12:37:44 A. Not in the context of a D-Arginine at the zero
12:37:46 position. D-Arginine in the prior art was known for
12:37:53 providing resistance to enzyme degradation, so there would
12:37:53 be no need to provide that with an additional group with the
12:37:58 P or Z position.
12:37:59 Q. If you didn't have a D-Arginine at the P or Z
12:38:04 position, did the prior art disclose any potential role for
12:38:07 the protecting groups listed for Z in Claim 1 of the '7,803
patent for improving enzyme resistance?
12:38:12 A. Yes, in that case you might expect a person of skill
12:38:16 in the art would have expected that the existence of one of
12:38:19 these groups on the N-terminus in the absence of the D-Arg
12:38:26 you would need to provide resistance.
12:38:26 Q. Would you use any of those groups in addition to
12:38:27 D-Arginine for enzyme resistance?
12:38:31 A. No, there would be no reasons to use D-Arg and one of
12:38:35 the other groups on the N-terminus.
12:38:39 Q. Let's go to DDX2-78. This is another excerpt from the
12:38:45 '963 patent we talked about earlier. That is JTX-38. Up on
12:38:53 the slide you have Table 2. Can you explain what's shown in
12:38:56 Table 2?
12:38:58 A. Yes, Table 2 again shows the sequence as we have been
12:39:02 talking about, of bradykinin and like peptides.

12:39:07 Q. **What is shown at the zero position at that sequence in**
12:39:12 **Table 2?**
12:39:12 A. **We have an N at the position to indicate substitution**
12:39:17 **at that position.**
12:39:18 Q. **Is the N defined in the text below Table 2?**
12:39:21 A. **Yes. Here N is defined as you see it as anhydrous or**
12:39:27 **acidic, basic or neutral aromatic amino acid residue of the**
12:39:31 **D or L configuration such as D-Arg, D-Lys, L-thienylalanine,**
12:39:40 **or an N-terminal enzyme protecting group selected from the**
12:39:44 **group comprising acyl-type protecting groups, aromatic**
12:39:50 **urethane-type protecting groups, alkyl type protecting**
12:39:54 **groups, or, alternatively, N is a di- or polypeptide**
12:39:59 **containing amino acids of the D or L configuration, such as**
12:40:01 **the ones listed.**
12:40:02 Q. **Does this text suggest the use of D-Arginine and the**
12:40:07 **N-terminal groups that are listed at the same time?**
12:40:10 **MS. KUZMICH: Your Honor, I have an objection**
12:40:12 **here that this opinion is not in either of the doctor's**
12:40:17 **expert reports, this particular opinion about this passage**
12:40:22 **and the explanation of the alternative, it is not there in**
12:40:28 **either of his expert reports.**
12:40:29 **THE COURT: Counsel.**
12:40:32 **MR. JAMES: Your Honor, I disagree. He talked**
12:40:34 **about the '963 --**
12:40:35 **THE COURT: If the two of you can compare, speak**

12:40:39 off line.

12:41:00 (Pause.)

12:42:46 MR. JAMES: Your Honor, if I may, the objection

12:42:48 seems to be that although he talked about his opinions with

12:42:52 respect to --

12:42:57 MS. KUZMICH: We have a broad disclosure to the

12:42:59 '963, Your Honor. But we don't have this particular passage

12:43:03 analyzed.

12:43:04 THE COURT: Is that true?

12:43:05 MR. JAMES: I don't --

12:43:07 THE COURT: Is it true?

12:43:08 MR. JAMES: I don't --

12:43:10 THE COURT: Read the language. Where is it

12:43:12 analyzed?

12:43:13 MR. JAMES: It says the teachings of the '963

12:43:18 patent would motivate a POSA to remove the Fmoc or anything

12:43:20 through to the N-terminus of the bradykinin antagonist

12:43:24 peptide claimed in the '7,803 patent.

12:43:26 THE COURT: Contextually, can you say that

12:43:29 doesn't satisfy your objection?

12:43:31 MS. KUZMICH: I don't think it points to this

12:43:33 passage in the analysis, now that we have all of it

12:43:38 alternately and now providing an opinion you would only use

12:43:43 of those --

12:43:44 THE COURT: Was it in the doctor's report as to

12:43:47 **the passage known before his opinion?**

12:43:52 **MS KUZMICH: I would say no, it wasn't in his**

12:43:54 **deposition or his expert report.**

12:43:57 **THE COURT: If it is not disclosed, I would not**

12:44:02 **permit it, I don't permit it.**

12:44:06 **By the way, when did you get the slide?**

12:44:09 **MS. KUZMICH: Last night.**

12:44:09 **THE COURT: Did you know the slide was in it,**

12:44:11 **last night? Did you see it?**

12:44:14 **Did you think to dial up counsel instead of**

12:44:18 **wasting the Court's time? How long has he been on the**

12:44:24 **stand?**

12:44:24 **Let's take a recess. We will be back in an**

12:44:28 **hour.**

12:44:29 **(Luncheon recess taken.)**

13:25:56 **Afternoon Session, 1:47 p.m.**

13:47:45 **THE COURT: Counsel, please take your seats.**

13:47:47 **Did you work it out?**

13:47:48 **MR. JAMES: Yes, we did.**

13:47:49 **THE COURT: Good. Let's go.**

13:47:50 **BY MR. JAMES:**

13:47:56 Q. **Doctor Bachovchin, just to reorient where we were, on**

13:48:00 **slide DTX-2-78, there's a passage from the '963 patent. My**

13:48:07 **question was: Does this passage suggest the use of**

13:48:12 **D-Arginine and the other N terminal groups that are listed**

13:48:17 here at the same time?
13:48:18 A. No, it does not.
13:48:20 Q. Can you explain why not?
13:48:22 A. It indicates that you could have a D-Arginine or another N terminal protected group, but it does not indicate that you would put an N-terminal group on top of the D-Arginine.
13:48:36
13:48:37 Q. Now, let's go to the next part of the slide, Mr. Chase. We've overlaid the sequence of Fmoc-icatibant onto this slide.
13:48:39
13:48:44
13:48:48 Would this passage in the '963 patent motivate a person to leave on the Z group, the Fmoc?
13:48:50
13:48:54 A. No, it would not.
13:48:55 Q. Can you explain why not?
13:48:56 A. It would not because it has a D-Arginine in what we've been calling position zero, and once you have a D-Arginine in position zero, there would be no need to put on another N terminal protecting group.
13:49:02
13:49:05
13:49:08
13:49:10 Q. And why not just leave on the Z on top of the D-Arginine?
13:49:15
13:49:15 A. That would be extraneous. There would be no reason to do that.
13:49:18
13:49:19 Q. Okay. Let's go to the next slide.
13:49:24 Now, Dr. Bachovchin, actually, I'm sorry. Just hold up for a second. I want to summarize your opinions
13:49:28

13:49:31 now, if we could.

13:49:32 Have you formed an opinion as to whether claim
13:49:34 14 of the '333 patent is an obvious variant of Claim 1 of
13:49:38 the ''7,803 patent?

13:49:40 A. Yes, I have.

13:49:41 Q. And what is your opinion in that regard?

13:49:45 A. My opinion is that claim 14 of the '333 patent is an
13:49:51 obvious variant of Claim 1 of the ''7,803 patent.

13:49:54 Q. And let's put up the next slide. And using this
13:49:57 slide, I'm sorry, Mr. Chase. If we could put up DDX-2-79.
13:50:03 Thank you.

13:50:04 Could you summarize the bases for your opinions
13:50:09 for the Court, please?

13:50:10 A. Yes, I can. So the reasons for my opinion include
13:50:12 that the '7,803 and the '333 patents are co-owned and have
13:50:17 inventors in common. It also includes that the peptides
13:50:23 claimed in the '7,803 patent include the same ten amino acid
13:50:27 sequence recited in claim 14 of the '333 patent, with a
13:50:31 removable protecting group attached, as illustrated here in
13:50:36 this colored diagram.

13:50:39 Here, you can see that claim 14 of the '333
13:50:41 patent, its sequence is illustrated by these colored balls
13:50:45 with the three letter codes for each amino acid and the same
13:50:50 is illustrated for Claim 1 of the '7,803 patent. And if you
13:50:54 go through here, you can see that at each position, the

13:50:59 amino acids are identical, and the only difference between
13:51:03 Claim 1 of the '7,803 patent and claim 14 of the '333 patent
13:51:10 is the presence of the Fmoc group on the n-terminus of the
13:51:15 peptide.
13:51:16 Q. And what would the person of ordinary skill in the art
13:51:19 have been motivated to do with that Fmoc?
13:51:21 A. A person of ordinary skill in the art would be
13:51:23 motivated to remove that Fmoc.
13:51:25 Q. And what would be the result?
13:51:26 A. The result would be that the Claim 1 of the '7,803
13:51:30 patent would be exactly the same as claim 14 of the '333
13:51:35 patent.
13:51:36 Q. And what would be the expectation of the person of
13:51:39 skill in the art with respect to the remaining peptide after
13:51:42 the Fmoc is removed?
13:51:44 A. So a person of skill in the art would expect that
13:51:47 after the Fmoc group is removed, the peptide of Claim 1 of
13:51:53 the '7,803 patent would be a bradykinin antagonist. So the
13:51:59 peptide of claim 14 of the '333 patent is therefore an
13:52:04 obvious variant of Claim 1 in the '7,803 patent.
13:52:08 MR. JAMES: Your Honor, that's the end of his
13:52:10 testimony on obviousness-type double patenting, but as
13:52:15 Mr. Wiesen mentioned in his opening, Dr. Bachovchin has a
13:52:18 very short amount of testimony that we would like him to
13:52:21 give on secondary considerations so he would be out of

13:52:25 order. It's about five minutes worth. And I think he's
13:52:29 asking whether you object.
13:52:30 MS. KUZMICH: We have no objections.
13:52:31 THE COURT: Okay. All right. Thanks for the
13:52:36 interpretation, counsel.
13:52:37 BY MR. JAMES:
13:52:41 Q. I want to talk briefly about the formulation of the
13:52:43 prior art Stewart compound and icatibant. Let's look at
13:52:48 DTX-50. Is this an article by Wirth and his colleagues?
13:52:56 A. Yes, it is.
13:52:58 Q. When was the Wirth article published?
13:53:00 A. This article was published in 1991.
13:53:03 Q. And just to be clear, Dr. Bachovchin, did you rely on
13:53:07 Wirth in forming your opinions on obviousness-type double
13:53:09 patenting?
13:53:10 A. No, I did not.
13:53:11 Q. Now, let's look at the title. It refers to something
13:53:14 called Hoe 140. What is that?
13:53:18 A. Hoe 140 is, in fact, icatibant.
13:53:22 Q. Does the Wirth article compare formulations of
13:53:27 icatibant and a prior art Stewart bradykinin antagonist
13:53:31 peptide?
13:53:31 A. Yes, it does.
13:53:32 Q. Let's look at, Mr. Chase, if you could put up the
13:53:35 second paragraph of the introduction, please. And let's

look at the first sentence.

And, Dr. Bachovchin, what types of models was Hoe 140 being tested in?

A. So Hoe 140 is being tested in in vivo models where bradykinin is serving as an agonist.

Q. And let's skip down a sentence, and if you could, tell us what compound Hoe 140 was being compared to in these tests?

A. So the prior art compound that's being compared to icatibant is shown here and numbered the way we have defined already. This is the bradykinin antagonist and it is a bradykinin in sequence in which you have D-Arginine on the n-terminus, hydroxyproline in addition to thienylalanine in positions five and eight and D-Phe in position seven.

Q. Was that compound disclosed in the prior art?

A. Yes, it was.

Q. Which prior art was it disclosed in?

A. Several places, including disclosed in Vavrek and Stewart in 1985 and disclosed in a patent application.

Q. Was it disclosed in the '993 patent?

A. '993 patent.

Q. Let's look at the third paragraph in the right column of Wirth. Now, in this passage, does Wirth describe the formulation of icatibant and the prior art Stewart peptide for subcutaneous administration?

13:55:12 A. **Yes, he does.**

13:55:13 Q. **And if we could put up page DTX-50-2, Mr. Chase. I**
13:55:24 **think we have that. It's the paragraph in the left column.**
13:55:31 **Thank you.**

13:55:31 **And does Wirth describe here the formulation of**
13:55:37 **icatibant and the prior art Stewart peptide for IV**
13:55:40 **administration?**

13:55:41 A. **Yes, he does.**

13:55:42 Q. **And does Wirth describe any differences in the way in**
13:55:46 **which icatibant and the prior art Stewart peptide are**
13:55:50 **formulated?**

13:55:51 A. **No, no differences are described.**

13:55:52 Q. **Does Wirth describe any differences in the stability**
13:55:56 **of the formulation of the icatibant and the prior art**
13:56:00 **Stewart peptide?**

13:56:00 A. **No. No differences of stability are described between**
13:56:04 **icatibant and the prior art compound.**

13:56:06 Q. **Mr. Chase, could you put up the last page, Page 4 the**
13:56:09 **next-to-last paragraph of the paper.**

13:56:12 **And here, Dr. Bachovchin, does Wirth compare**
13:56:16 **the tolerability of icatibant and the prior art Stewart**
13:56:20 **peptide?**

13:56:20 A. **Yes, he does.**

13:56:21 Q. **Does he describe any significant differences in the**
13:56:25 **tolerability of the two peptides?**

13:56:27 A. **No. He describes no significant differences in the**
13:56:29 **tolerability of the two peptides.**
13:56:32 Q. **Now, in this Wirth paper and the other references**
13:56:34 **you've looked at, have you seen any evidence of differences**
13:56:38 **in formulation, stability or tolerability between icatibant**
13:56:42 **and the prior art Stewart compounds?**
13:56:43 A. **I have not seen any differences in formulation**
13:56:46 **stability or tolerability of icatibant versus the prior art**
13:56:51 **Stewart compound.**
13:56:53 **MR. JAMES: I have no further questions, your**
13:56:55 **Honor.**
13:56:55 **THE COURT: All right. You may cross-examine.**
13:56:57 **MS. KUZMICH: Yes. Permission to cross-examine?**
13:56:59 **THE COURT: Yes.**
13:56:59 **MS. KUZMICH: Permission to approach the bench**
13:57:02 **with material?**
13:57:02 **THE COURT: Yes.**
13:57:03 **MS. KUZMICH: And the witness?**
13:57:04 **THE COURT: You have that.**
13:57:05 **MS. KUZMICH: Thank you.**
13:57:09 **THE COURT: Counsel, remind me of your name.**
13:57:13 **MS. KUZMICH: Sandra Kuzmich.**
13:57:14 **THE COURT: Okay. Thank you.**
13:57:16 **MS. KUZMICH: Thank you, your Honor.**
13:57:33 **(Ms. Kuzmich handed binders to the Court and to**

13:57:37 the witness.)

13:58:23 MS. KUZMICH: Permission to proceed, your Honor?

13:58:24 THE COURT: Yes.

13:58:25 MS. KUZMICH: Thank you.

13:58:27 THE COURT: If you want to turn that thing toward the witness, that podium moves.

13:58:30 MS. KUZMICH: Oh, okay. Thank you.

13:58:32 THE COURT: It's up to you.

13:58:33 CROSS-EXAMINATION

13:58:33 BY MS. KUZMICH:

13:58:34 Q. Good afternoon, Dr. Bachovchin.

13:58:36 A. Good afternoon.

13:58:36 Q. My name is Sandra Kuzmich and I am from the law firm of Haug Partners, and we represent the plaintiffs here today, Shire and Sanofi. And I'm going to ask you some questions about the opinions you've provided today as well as some opinions you've provided throughout the case.

13:58:53 I've handed you a binder of materials. I think most you've seen before, but feel free to reference them and what we're going to try to do is put a lot of these things on the screen so it will be easier for you to follow.

13:59:06 Doctor, if you could turn to DTX-59, which is the '7,803 patent. I'm going to call that up on the screen. And if you can refer to Claim 1, and that is at column 20.

13:59:46 **And, Doctor, we have that on the screen, Claim 1 of the '7,803 patent. And it's the case that you came to a conclusion as to the meaning of Claim 1 of the '7,803 patent; is that correct?**

A. **Yes, that's correct.**

Q. **In coming to your opinion as to the meaning of the '7,803 patent, Claim 1, did you consider the specification of the '7,803 patent?**

A. **I did not.**

Q. **In coming to your opinion as to the meaning of Claim 1 of the '7,803 patent, did you consider the prosecution history of the '7,803 patent?**

A. **I did not.**

Q. **In looking at the peptides of Claim 1 of the '7,803 patent, does that, does Claim 1 encompass peptides that are attached to a solid phase synthesis support resin?**

A. **It does not.**

Q. **And, Doctor, if you could turn your attention to the A component of Claim 1 of the '7,803 patent. Does the A component, those amino acids, encompass amino acids that are protected at their side chain?**

A. **It does not.**

Q. **And for component B, does that component encompass protection of the arginine residue at the side chain?**

A. **No, it does not.**

14:01:02 Q. **And for component C, does that encompass protection of**
14:01:05 **the amino acid side chain?**
14:01:07 A. **It does not.**
14:01:08 Q. **And for component E, does that encompass protection of**
14:01:13 **the amino acid thienylalanine, amino acid at the side chain?**
14:01:19 A. **It does not.**
14:01:20 Q. **And for component F, does that encompass protection of**
14:01:24 **the amino side chain of serine?**
14:01:26 A. **It does not.**
14:01:26 Q. **And for element Q, does that element encompass**
14:01:30 **protection at the amino acid side chain?**
14:01:33 A. **It does not.**
14:01:34 Q. **And for component G, does that encompass protection of**
14:01:37 **the amino acid side chain?**
14:01:39 A. **No, it does not.**
14:01:40 Q. **And, finally, for component F prime, Doctor, does that**
14:01:44 **encompass protection at the amino acid side chain?**
14:01:47 A. **No, it does not.**
14:01:49 Q. **If you could focus your attention, Doctor, at page**
14:01:53 **DTX-59.10, and that would be at column 18, lines 44 through**
14:01:59 **45, which is Example 1.**
14:02:04 **And my question: As it appears at column 18,**
14:02:15 **lines 44 through 45, is this peptide encompassed by example,**
14:02:20 **or Claim 1 of the '7,803 patent?**
14:02:23 A. **I'm sorry. What column are we on? Column 10, did you**

14:02:26 say?
14:02:26 Q. We are at column 18, lines 44 to 45.
14:02:30 A. Okay.
14:02:31 Q. And it's DTX-59 at Page 10.
14:02:37 A. Page 10. DTX-59. Example 1. Okay. I've got it.
14:02:46 Q. Yes. And my question is: Is the peptide in Example 1
14:02:50 encompassed by Claim 1 of the '7,803 patent?
14:02:53 A. Yes, it is.
14:02:54 Q. And as it appears at Column 18, lines 44 to 45, is the
14:03:00 peptide of Example 1 attached to a solid phase peptide
14:03:04 synthesis support resin?
14:03:08 A. No, it's not.
14:03:09 Q. And as it appears at column 18, line 44 through 45,
14:03:13 does the peptide in Example 1 have side chain protecting
14:03:17 groups?
14:03:17 A. No, it does not.
14:03:19 Q. Doctor, if we could turn our attention to the Z group
14:03:32 of Claim 1 of the '7,803 patent. And if you could turn back
14:03:37 to Claim 1, which is at Column 20.
14:03:44 And so a person of ordinary skill in the art
14:03:47 just looking at Claim 1 of the '7,803 patent would
14:03:51 understand that the purpose of the Z group could be for
14:03:55 multiple reasons; is that correct?
14:03:56 A. That's correct.
14:03:57 Q. And when a person of ordinary skill in the art looks

14:04:00 **at Claim 1 of the '7,803 patent, does a person of ordinary**
14:04:03 **skill in the art think that the Z group should be removed?**
14:04:07 A. **I'm not sure I understand what you mean by should be**
14:04:12 **removed. A person of ordinary skill in the art would**
14:04:20 **understand that it could be removed.**
14:04:22 Q. **So would the person of ordinary skill in the art**
14:04:25 **presume that the Z group was there left over from synthesis?**
14:04:33 A. **Not in every case.**
14:04:34 Q. **Would the person of ordinary skill in the art presume**
14:04:36 **that you could remove it and that you would get the desired**
14:04:38 **peptide that you wanted?**
14:04:40 A. **Not in every case.**
14:04:42 Q. **So, Doctor, we're going to take a look at your**
14:04:49 **deposition transcript, and if we could take a look at Page**
14:04:54 **251, line 20.**
14:04:58 **MR. JAMES: Objection, your Honor.**
14:04:59 **THE COURT: This isn't how we do this in my**
14:05:01 **courtroom. Do you have copies of the transcript?**
14:05:03 **MS. KUZMICH: Yes. In the binders, your Honor.**
14:05:04 **THE COURT: All right. Why don't you direct the**
14:05:06 **witness to, and everybody. You're going to object it's not**
14:05:12 **impeachment?**
14:05:12 **MR. JAMES: Yes, your Honor.**
14:05:13 **THE COURT: Let's get a little --**
14:05:16 **MR. JAMES: Yes.**

14:05:17 **THE COURT: Do you see it, Doctor? It occurs in your binder. It has your name and deposition.**

14:05:27 **What page and what lines?**

14:05:29 **MS. KUZMICH: If we would turn to Page 251, line 20, to 252, line 5.**

14:05:42 **THE COURT: 251, line 20, to what?**

14:05:45 **MS. KUZMICH: 251, line 20.**

14:05:49 **THE COURT: To?**

14:05:49 **MS. KUZMICH: To 252, line 5.**

14:05:51 **THE COURT: Read that to yourself, Doctor.**

14:06:04 **THE WITNESS: I'm having trouble finding it. Page 252?**

14:06:09 **THE COURT: The pages are on the top right-hand corner.**

14:06:16 **THE WITNESS: I don't see the page numbers. Okay. I see it. Okay.**

14:06:32 **THE COURT: Again, let's give him the lines again. 251?**

BY MS. KUZMICH:

14:06:37 Q. **251, line 20, Doctor.**

14:06:39 A. **Yes.**

14:06:40 Q. **To 252, line 5.**

14:06:42 **THE COURT: Read those to yourself.**

14:06:46 **THE WITNESS: Okay. I will read it to myself.**

14:06:48 **(Pause.)**

14:07:08 **THE WITNESS: Yes. Okay. I see that.**

14:07:10 **THE COURT: Is there still an objection?**

14:07:13 **MR. JAMES: I don't think that there has been a question asked that she's trying to impeach him on.**

14:07:15

14:07:17 **THE COURT: Not yet. I saw you rise earlier.**

14:07:21 **MR. JAMES: Yes.**

14:07:22 **THE COURT: Are you anticipating an objection?**

14:07:23 **MR. JAMES: I was objecting that she was pointing him to his deposition transcript when she hadn't asked a question as a predicate to impeach him.**

14:07:25

14:07:28

14:07:30 **THE COURT: Fair. Very well. That's technically a correct objection. But now we're there. Go ahead and ask the question.**

14:07:32

14:07:35

14:07:37 **BY MS. KUZMICH:**

14:07:37 Q. **So my question, Doctor, is: So a person of ordinary skill in the art just looking at Claim 1 of the '7,803 patent would understand that the purposes of the Z group could be for multiple reasons; is that correct?**

14:07:40

14:07:43

14:07:49

14:07:52 A. **Yes, that's correct.**

14:07:53 Q. **And then when a person of ordinary skill in the art looks at Claim 1 of the '7,803 patent, does a person of ordinary skill in the art think that the Z group should be removed?**

14:07:55

14:07:59

14:08:02

14:08:03 A. **I -- a person of ordinary skill in the art would look at the Z group as a group that could be removed.**

14:08:07

14:08:11 Q. **And, Doctor, is that the same answer that you are**
14:08:18 **giving, gave me at the deposition?**
14:08:21 **MR. JAMES: Objection, your Honor.**
14:08:22 **THE COURT: Sustained. I will be the judge of**
14:08:29 **that.**
14:08:30 **BY MS. KUZMICH:**
14:08:30 Q. **Doctor, I'm asking you: Should the person -- would**
14:08:33 **the person of ordinary skill in the art think that the Z**
14:08:35 **group should be removed when looking at Claim 1 of the**
14:08:39 **'7,803 patent?**
14:08:40 A. **If a person of ordinary skill in the art would look at**
14:08:44 **the Z group and think that it could very well be left over**
14:08:48 **from synthesis and would therefore think that it should be**
14:08:51 **removed, then certainly they would think that it could be**
14:08:53 **removed.**
14:08:54 **THE COURT: Counsel, I'm missing your point. I**
14:08:55 **want to make sure I get it.**
14:08:57 **He does actually use the language that you could**
14:08:59 **remove. He says you could remove.**
14:09:01 **MS. KUZMICH: I think, your Honor, I was**
14:09:03 **wondering, I was trying to get to the point, was -- the**
14:09:08 **doctor said that the person of ordinary skill in the art**
14:09:10 **would presume that the Z group was there left over from**
14:09:14 **synthesis.**
14:09:16 **THE COURT: Well, actually, you asked two**

14:09:19 questions. The first had to do with should and could and I
14:09:22 was addressing the should and could.
14:09:24 In our you second question is?
14:09:25 MS. KUZMICH: Would the person of ordinary skill
14:09:27 in the art presume that the Z group was there left over from
14:09:30 synthesis when looking at Claim 1 of the '7,803 patent and
14:09:35 the Z group.
14:09:35 THE COURT: And where is the asserted
14:09:37 inconsistency?
14:09:38 MS. KUZMICH: I didn't hear him say at all that
14:09:40 the person of ordinary skill in the art would presume that
14:09:43 the Z group was left over from synthesis.
14:09:45 THE COURT: Why don't you explain that, Doctor.
14:09:47 THE WITNESS: Okay. So a person of ordinary
14:09:53 skill in the art would look at, would first look. He might
14:09:59 presume it was left over from synthesis, but he certainly
14:10:02 would know or think that it could be removed.
14:10:07 BY MS. KUZMICH:
14:10:08 Q. When a person of ordinary skill in the art sees the Z
14:10:11 groups that are listed in Claim 1 of the '7,803 patent, does
14:10:15 the person of ordinary skill in the art think that all of
14:10:18 those Z groups could be removed without damaging the peptide
14:10:23 backbone?
14:10:24 A. All of those groups could be removed with various
14:10:26 effects on the peptide backbone depending on the Z group

14:10:32 that's there.
14:10:33 Q. Doctor, if we could turn to JTX-15 in your binder, and
14:10:40 we'll call that up on the screen. And it's page JTX-15.31.
14:10:50 A. JTX-15?
14:10:53 Q. At JTX-15.31.
14:11:02 A. JTX-15.31?
14:11:05 THE COURT: Look in the middle. You'll see JTX
14:11:07 and the numbers.
14:11:08 THE WITNESS: So 31. 15.31. Okay.
14:11:31 BY MS. KUZMICH:
14:11:31 Q. And, Doctor, if you would focus your attention to the
14:11:34 very bottom of the screen, and I will read those sentences
14:11:36 into the record. Several simple amine-protecting groups
14:11:41 derived from carboxylic acids and commonly used in organic
14:11:45 synthesis are obviously not suitable in peptide synthesis.
14:11:48 For instance, acetylation or benzoylation of amino groups is
14:11:54 impractical, because the vigorous hydrolysis needed for
14:12:00 deacylation cleaves peptide bonds as well.
14:12:01 Did I read that correctly?
14:12:02 A. Yes, you did.
14:12:03 Q. Dr. Bachovchin, based on the second sentence I just
14:12:06 read aloud from JTX-15.31, wouldn't a person of ordinary
14:12:10 skill in the art understand that acetyl groups or benzoyl
14:12:15 groups as N protecting groups on peptides would not be
14:12:18 considered ideal as protecting groups in synthesis because

14:12:21 removal could destroy the peptide bond?
14:12:31 A. These protecting groups would not be ideal for
14:12:34 repeated use in the synthesis of peptide. You may very well
14:12:38 want to use them in the last step for specific purposes.
14:12:41 There may be a case where you want an unusual protecting
14:12:44 group on the n-terminus to protect the other protecting
14:12:47 groups during the procedure and you may have decided that
14:12:51 you are not going to remove those protecting groups, but the
14:12:54 fact that they are not removed does not mean you could not
14:12:57 make a peptide again in the absence of that protecting
14:13:00 group.
14:13:03 Q. And, Doctor, if you could turn back to DTX-59 at page
14:13:07 DTX-59.11, focusing again on Claim 1 of the '7,803 patent.
14:13:22 A. Yes. Okay.
14:13:27 Q. And are any of the Z groups identified there at column
14:13:33 one of the '7,803 patent, acetyl groups?
14:13:37 A. Yes.
14:13:39 Q. Which ones are they?
14:13:40 A. All of them except for the Fmoc group.
14:13:43 Q. And are any of them benzoyl groups?
14:13:47 A. The last one clearly is a benzoyl group.
14:13:53 Q. So 10 out of the 11 groups in the Z category would
14:13:57 fall under the category of acetylation or benzoylation that
14:14:01 we looked at from the Bodanszky reference, JTX-15.31; is
14:14:07 that right?

14:14:07 A. **Yes, that's correct.**

14:14:08 Q. **And if we stay in Claim 1 of the '7,803 patent and**
14:14:14 **maybe focus our attention on the P group. Isn't it your**
14:14:20 **opinion that a person of ordinary skill in the art would**
14:14:22 **have focused on P being a direct linkage rather than an**
14:14:26 **additional amino acid because the amino acids listed in P**
14:14:30 **are optional and therefore less significant?**

14:14:35 A. **The fact that the P group is optional would indicate**
14:14:38 **to a person of ordinary skill in the art they're probably**
14:14:41 **less significant for the desired biological properties.**

14:14:44 Q. **And isn't it your opinion that a person of ordinary**
14:14:45 **skill in the art would have viewed the '7,803 patent Claim 1**
14:14:50 **first as a ten amino acid peptide with an attached N**
14:14:55 **terminal protecting group on the N terminal D-Arg and,**
14:14:59 **secondarily, as an 11 amino acid peptide, including one of**
14:15:03 **the optional amino acids?**

14:15:05 A. **Yes. I think a person of skill in the art would view**
14:15:12 **A through I as defining the amino acid peptide and you could**
14:15:19 **have a P group that would represent the 11th amino acid.**

14:15:22 Q. **Doctor, if you would please turn to DTX-60 in your**
14:15:28 **binder, and focus on Page 1 of DTX-60.**

14:15:45 **Is this a document, Doctor, that you reviewed in**
14:15:48 **the course of the litigation?**

14:15:49 A. **Yes, it is.**

14:15:50 Q. **So on the first page of DTX-60.1 or underscore one,**

14:15:56 **on the right-hand column under the heading synthesis of**
14:15:59 **AP III --**
14:16:01 A. **Yes.**
14:16:01 Q. **-- it identifies two ways to make the peptide AP III;**
14:16:06 **is that correct?**
14:16:06 A. **It appears to, yes.**
14:16:10 Q. **Is the first method by solution phase synthesis?**
14:16:14 A. **Yes.**
14:16:14 Q. **Is the second phase by, second approach by solid phase**
14:16:18 **synthesis?**
14:16:19 A. **Yes, it is.**
14:16:20 Q. **Would you please turn to scheme one at page DTX-60.2.**
14:16:29 **So that's Page 2.**
14:16:31 A. **DTX-60 -- I'm sorry. What page?**
14:16:37 Q. **It's still the same document?**
14:16:38 A. **Page 2. Okay.**
14:16:40 Q. **And if you would focus your attention at the reaction**
14:16:43 **at the second arrow from the top.**
14:16:47 A. **Yes.**
14:16:48 Q. **That reaction represents removal of the Fmoc group**
14:16:51 **from the N terminal amino acid; is that correct?**
14:16:53 A. **That's correct.**
14:16:54 Q. **And the peptide from which Fmoc is removed at that**
14:16:58 **arrow has side chain protecting groups on it; is that**
14:17:02 **correct?**

14:17:02 A. **That's correct.**

14:17:02 Q. **And would you please identify the side chain protecting groups that were on the peptide when Fmoc was removed?**

14:17:05 A. **Those are two tert butyl.**

14:17:09 Q. **Now, if you would focus your attention at the reaction from the fourth arrow from the top at the scheme and does that reaction represent removal of the Fmoc group from the N terminal amino acid?**

14:17:12 A. **Yes, it does.**

14:17:15 Q. **And doesn't that peptide from which the Fmoc is removed at the fourth arrow have side chain protecting groups on it?**

14:17:18 A. **Yes, it does.**

14:17:22 Q. **If you would focus your attention on the sixth arrow from the reaction scheme, that reaction is removal again of the Fmoc group from the N terminal amino acid; is that correct?**

14:17:23 A. **That's correct.**

14:17:24 Q. **And upon removal or when that reaction is carried out, there are side chain protecting groups on the peptide; is that correct?**

14:17:27 A. **That's correct.**

14:17:30 Q. **And if you would focus your attention on the eighth arrow down from the top of the scheme, that reaction also is**

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14:17:58 **removal of the Fmoc group; is that correct?**

14:18:01 A. **That's correct.**

14:18:01 Q. **And on that peptide from which the Fmoc is removed, isn't it the case that there are side chain protecting groups on the peptide?**

14:18:08

14:18:10 A. **That's correct.**

14:18:11 Q. **So isn't it the case that every time the Fmoc was removed from a peptide in scheme one at DTX-60, Page 2, that full peptide contains side chain protecting groups?**

14:18:14

14:18:21

14:18:25 A. **In this case, that's the case, yes.**

14:18:26 Q. **If you would turn to scheme two of DTX-60 and that's at DTX-60, Page 4. And we have that brought up on the screen.**

14:18:30

14:18:36

14:18:41 **And, Doctor, does this represent a solid phase peptide synthesis?**

14:18:45

14:18:46 A. **Yes, it does.**

14:18:49 Q. **And looking at the first arrow of the scheme, isn't it the case that step one there, the treatment of 20 percent piperidine in DMF removes the Fmoc group that is bound to the growing peptide?**

14:18:54

14:18:57

14:19:05

14:19:05 A. **That's the case, yes.**

14:19:07 Q. **And at that first arrow, there's a phrase, 26 cycles.**

14:19:11 **Do you see that? I'm sorry. I apologize. It's 23 cycles.**

14:19:19

14:19:20 A. **Yes. I see 23 cycles, yes.**

14:19:22 Q. **What does that mean?**

14:19:23 A. **It means that the Fmoc has been removed 23 times.**

14:19:27 Q. **And in each case that the Fmoc was removed, the peptide is on the resin and contains side chain protecting groups. Isn't that correct?**

14:19:35 A. **Yes. That's one of the advantages of Fmoc, that it can be removed repeatedly without disrupting the other chemistry that is going on.**

14:19:43 Q. **And looking at the peptide, the long peptide in the middle of the scheme, Doctor, isn't it the case that that peptide is protected by Fmoc at the n-terminus and side chain protecting groups and is also attached to the resin?**

14:20:00 A. **Yes, that's the case.**

14:20:07 Q. **And the first step in the reaction scheme of the arrow underneath that peptide is treatment with 20 percent piperidine in DMF; is that correct?**

14:20:18 A. **That's correct.**

14:20:19 Q. **And what would be the result of the treatment of 20 percent piperidine DMF?**

14:20:25 A. **It would remove the Fmoc group without disturbing the other blocking groups.**

14:20:30 Q. **So isn't it the case, Doctor, that in every reaction that we looked at in DTX-60, every time the Fmoc was removed, it's either on the resin and/or has side chain protecting group?**

14:20:43 A. **Yes.**

14:20:44 Q. **Doctor, if you could turn to JTX- 16 in your binder.**

14:21:00 **Now, Doctor, did you review JTX- 16 in the**

14:21:03 **course of your work for this litigation?**

14:21:05 A. **Yes, I did.**

14:21:05 Q. **And if you would turn to JTX-16.2. There's depicted a**

14:21:11 **solid phase peptide synthesis scheme.**

14:21:17 **Do you see that?**

14:21:17 A. **Yes, I do.**

14:21:18 Q. **And referring to the third arrow down in reaction**

14:21:21 **scheme, does that represent removal of Fmoc from the**

14:21:23 **N-terminus of a peptide where the peptide is bound to the**

14:21:26 **resin during synthesis?**

14:21:28 A. **Yes, it does.**

14:21:30 Q. **And if you look one step down, you will see kind of a**

14:21:36 **squiggly line where it says several cycles?**

14:21:38 A. **Yes.**

14:21:38 Q. **And what does that represent here?**

14:21:40 A. **Well, it means that the process has gone through**

14:21:46 **several cycles to build up the peptide.**

14:21:49 Q. **And so in those several cycles, each time before**

14:21:54 **another amino acid is added, the Fmoc would be removed; is**

14:21:58 **that correct?**

14:21:58 A. **That's the way that's used in Fmoc solid-phase peptide**

14:22:00 **synthesis, yes.**

14:22:04 Q. **And so the result underneath the several cycles, you**
14:22:06 **have a peptide that has Fmoc at the N-terminus, protecting**
14:22:10 **groups on the amino acids on the side chains, and it's also**
14:22:15 **bound to the resin; is that correct?**
14:22:16 A. **That's correct.**
14:22:17 Q. **And the next step where the arrow, the peptide is**
14:22:22 **labeled six, but there's an arrow where you see 55 percent**
14:22:26 **TFA in CH2CL2, one hour.**
14:22:31 **Do you see that?**
14:22:31 A. **I do.**
14:22:32 Q. **What does that reaction do?**
14:22:33 A. **That's removing the Fmoc group. It appears to be**
14:22:37 **removing some of the other side chains.**
14:22:39 Q. **And how do you see that as removing the Fmoc group,**
14:22:44 **doctor?**
14:22:44 A. **I'm sorry. My eyes played a trick on me. It leaves**
14:22:49 **the Fmoc on, removing the side chains without removing the**
14:22:52 **Fmoc.**
14:22:52 Q. **So what that reaction does is it removes the growing**
14:22:57 **peptide chain off of the resin and you're left with an Fmoc**
14:23:01 **protected peptide and also side chain protection; is that**
14:23:04 **correct?**
14:23:04 A. **Some of the side chains are protected. Some of them**
14:23:07 **you notice have been removed.**
14:23:09 Q. **And then the next step you'll see three steps. The**

14:23:14 **first one is 50 percent piperidine in DMF.**

14:23:18 **Do you see that?**

14:23:19 A. **Yes.**

14:23:19 Q. **And what will that do?**

14:23:21 A. **Well, that will remove the Fmoc.**

14:23:23 Q. **And so in that case, when the Fmoc is removed, the tertbutyl side chains on the cysteine are still in place; is that correct?**

14:23:31 A. **That's correct.**

14:23:32 Q. **And so every time the Fmoc was removed in this reaction scheme, there was, the peptide was either on the resin or had side group, side group protection; is that correct?**

14:23:45 A. **In this case, that's correct.**

14:23:50 Q. **Doctor, if you would turn to DTX-15 in your binder.**

14:24:22 A. **Okay.**

14:24:23 Q. **And did you review this document in the course of your work for this litigation?**

14:24:27 A. **I believe I did.**

14:24:32 Q. **If you could turn to DTX-15 at page 13 at column 23, line five, which begins, Example 2 of the 555 -- the '755 patent. And if you would turn your attention to lines 15 through 22, which appear under the structure of the peptide to be synthesized.**

14:25:03 **And does that passage, Doctor, indicate that the**

14:25:10

14:25:14 **peptide to be synthesized is being synthesized by an Fmoc**
14:25:18 **method?**
14:25:18 A. **Yes.**
14:25:20 Q. **And if you could look further down at column 23,**
14:25:25 **beginning at line 33. The '755 patent states that it's**
14:25:33 **providing a typical synthesis cycle. Is that correct?**
14:25:37 A. **At the moment, I don't see the passage. It's on page**
14:25:46 **13. Right?**
14:25:47 Q. **So we are on page 13 and it's column 23?**
14:25:51 A. **Yes.**
14:25:55 Q. **And we're beginning at line 33. And you have that**
14:25:59 **highlighted on the screen.**
14:26:02 A. **Typical synthesis -- got it.**
14:26:07 Q. **And the first step in that typical Fmoc synthesis**
14:26:11 **cycle is, one, elimination of the Fmoc group with 20 percent**
14:26:17 **piperidine in DMF, two times eight ml, ten minutes each.**
14:26:23 **Do you see that?**
14:26:24 A. **Yes.**
14:26:24 Q. **And what does that represent?**
14:26:29 A. **Well, there's a procedure for eliminating the Fmoc**
14:26:34 **group.**
14:26:34 Q. **And then if you could step down and read -- I will**
14:26:40 **read that for you. Read aloud the sentence that begins at**
14:26:44 **line 66 of column 23 of the '755 patent.**
14:26:49 **After the synthesis was complete, first the Fmoc**

14:26:52 **protective group was eliminated from the peptide-resin by**
14:26:56 **treatment with 20 percent piperidine in DMF, and the resin**
14:27:02 **was thoroughly washed with DMF and shrunk by treatment**
14:27:05 **several times with isopropanol and methyl tert.-butyl ether.**
14:27:14 **Do you see that?**
14:27:14 A. **Yes.**
14:27:15 Q. **Isn't it the case that when the Fmoc was removed from**
14:27:17 **this peptide, it was still on the resin and it also had**
14:27:21 **other protecting groups?**
14:27:23 A. **In this case, that's correct.**
14:27:31 Q. **So isn't it the case, Doctor, that in every situation**
14:27:38 **that we just looked at in the three documents, the three**
14:27:40 **references, the only time Fmoc was removed was when it was**
14:27:45 **on the peptide and/or it had on the peptide resin with side**
14:27:53 **chain protecting groups?**
14:27:54 A. **In the cases that we looked at here, that is true.**
14:27:57 Q. **And, so, Doctor, if we could call up your**
14:28:04 **demonstrative DDX-2-28. If we could bring that up.**
14:28:18 **And, Doctor, this is your demonstrative that you**
14:28:19 **created, DDX-2-28; is that correct?**
14:28:23 A. **Yes.**
14:28:24 Q. **So the way you represented it here, the peptide is not**
14:28:28 **on the resin; is that correct?**
14:28:29 A. **That's correct.**
14:28:30 Q. **And the way you've represented it here, none of the**

14:28:34 amino acids have side chain protecting groups; is that
14:28:37 right?
14:28:37 A. That's correct.
14:28:38 Q. So the way you've represented it here is not the same
14:28:43 as any of the materials we just went through; is that
14:28:46 correct?
14:28:46 A. That's correct.
14:28:48 Q. And if we could call up DDX-2-57.
14:29:03 And so this is your demonstrative DDX-2-57;
14:29:07 isn't that correct, doctor?
14:29:08 A. Yes, it is.
14:29:10 Q. And what you have shown here is Fmoc-icatibant being
14:29:14 treated with piperidine and then resulting in icatibant; is
14:29:19 that correct?
14:29:19 A. That's correct.
14:29:20 Q. And in none of the cases that we looked at from the
14:29:23 prior art literature was there a removal of Fmoc on a bare
14:29:31 bones peptide that was not on the resin with no side chain
14:29:34 protecting group; is that correct?
14:29:35 A. In the case we looked at, that is correct.
14:29:38 Q. And you have not identified for us anywhere, Doctor,
14:29:49 where you could show us examples where the Fmoc group was on
14:29:53 a peptide and not on a resin and didn't have side chain
14:29:55 protecting groups. Isn't that correct?
14:29:57 A. I don't recall that I did, but that's definitely a

14:30:00 possibility.

14:30:00 Q. But we don't have that here in our references in this

14:30:04 case, do we?

14:30:05 A. I don't recall that we do.

14:30:06 Q. Doctor, if you can turn to your binder in the document

14:30:12 JTX- 40.

14:30:32 A. Okay.

14:30:32 Q. And, Doctor, do you recognize this document?

14:30:35 A. Yes, I do.

14:31:06 Q. And this is one of the references that you relied on

14:31:09 in your, in preparing your opening expert report; is that

14:31:14 the case?

14:31:14 A. Yes, that's the case.

14:31:15 Q. And is it acceptable for you to refer to JTX- 40 as

14:31:21 the '204 patent?

14:31:23 A. Yes.

14:31:26 Q. Doctor, if you would please turn to Column 3, lines 1

14:31:30 to 10, at JTX-40.3.

14:31:43 Do you have that, Doctor?

14:31:44 A. I do.

14:31:45 Q. I will read that into the record. The term N-

14:31:48 protecting group as used herein refers to those groups

14:31:52 intended to protect the N-terminus against undesirable

14:31:56 reactions during synthetic procedures or to prevent the

14:31:59 attack of exopeptidases on the final compounds or to

14:32:05 **increase the solubility of the final compounds and includes**
14:32:08 **but is not limited to acyl, acetyl, pivaloyl, t-butylacetyl,**
14:32:17 **T-butyloxycarbonyl (Boc), carbobenzyloxycarbonyl, or benzoyl**
14:32:28 **groups or an L- or D-aminoacyl residue, which may itself be**
14:32:33 **N-protected similarly.**
14:32:34 **Do you see that?**
14:32:35 A. **Yes, I do.**
14:32:39 Q. **And the first reason that is provided here to put an N**
14:32:42 **protecting group on the N-terminus is to protect the**
14:32:44 **N-terminus against undesirable reactions as during synthetic**
14:32:48 **procedures; is that correct?**
14:32:49 A. **That's correct.**
14:32:50 Q. **And in that instance, in the instance, the N terminal**
14:32:54 **protecting group would be removed so that it's not part of**
14:32:56 **the final product; is that correct?**
14:32:58 A. **If that's the purpose, that would be normally the**
14:33:01 **case.**
14:33:05 Q. **And the second stated reason in the '204 patent at**
14:33:08 **Column 3, lines 1 to 10, to put an N protecting group on the**
14:33:10 **N-terminus is to prevent the attack of exopeptidases on the**
14:33:15 **final compound; is that correct?**
14:33:16 A. **That's correct.**
14:33:17 Q. **And in that instance, the N terminal protecting group**
14:33:20 **would not be removed, so it would remain as part of the**
14:33:23 **final compound?**

14:33:24 A. **That would normally be the case, yes.**

14:33:26 Q. **And one of the groups identified in the '204 patent as an N protecting group is a benzoyl group; is that correct?**

14:33:34 A. **Yes.**

14:33:34 Q. **And a benzoyl group was one of the Z groups identified in Claim 1 of the '7,803 patent; is that correct?**

14:33:40 A. **That's correct.**

14:33:42 Q. **Another one of the groups identified in the '204 patent at Column 3, line six, as an N protecting group is an N-acyl group. Is that correct? Is an acyl group? Excuse me.**

14:33:56 A. **Yes.**

14:33:56 Q. **Isn't it the case that Claim 1 of the '7,803 patent, the Z groups encompass acyl groups; is that correct?**

14:34:03 A. **That's correct.**

14:34:04 Q. **And one of the groups identified in the '204 patent at Column 3, Line seven, as an N protecting group is T-butyloxycarbonyl, otherwise known as BOC; isn't that correct?**

14:34:16 A. **Yes.**

14:34:16 Q. **As of 1989, BOC was known, used routinely as an N terminal protecting group in solid phase peptide synthesis; isn't that correct?**

14:34:26 A. **That's correct.**

14:34:27 Q. **And another group identified in the '204 patent at**

14:34:32 **Column 3, line 9, as an N protecting group is the**
14:34:35 **carbobenzyloxycarbonyl group; is that correct?**
14:34:40 A. **Yes.**
14:34:40 Q. **And as of 1989, wasn't the carbobenzyloxycarbonyl**
14:34:45 **group commonly used in peptide synthesis as an N-terminus**
14:34:50 **protecting group?**
14:34:51 A. **Commonly used. Not as commonly perhaps as Fmoc, but,**
14:34:56 **yes.**
14:34:58 Q. **And if you look at the passage at Column 3, lines 6 to**
14:35:01 **10, it does provide a non-exhaustive list of groups against**
14:35:05 **undesirable reactions during synthetic procedures, or also**
14:35:09 **to prevent attack from exopeptidases on the final compound;**
14:35:14 **isn't that correct?**
14:35:14 A. **Yes.**
14:35:21 Q. **So even though the Boc and the carbobenzyloxycarbonyl**
14:35:25 **group were used routinely in solid peptide synthesis as of**
14:35:28 **1989, they're also being suggested here at Column 3, lines 1**
14:35:32 **through 10 in JTX-40 as also being useful to prevent attack**
14:35:38 **against exopeptidases and therefore they would be left on**
14:35:42 **the final compound; is that correct?**
14:35:43 A. **I can't entirely agree with what you are saying there.**
14:35:48 **They would be left on the final compound if it was believed**
14:35:52 **that the final compound required them to be left on it.**
14:35:57 Q. **So if we could turn to example 14 of the '204 patent,**
14:36:01 **Doctor, and that is at JTX-40.5, column 8, lines 17 through**

14:36:10 **40. And we have that on the screen, Doctor.**

14:36:25 **And looking at the compound of Example 40,**

14:36:28 **doesn't the compound of example, sorry, excuse me, example**

14:36:31 **14 contain a Boc group?**

14:36:35 A. **Yes, it does.**

14:36:36 Q. **And is the Boc group bound to the N terminal amino**

14:36:44 **group of phenylalanine?**

14:36:47 A. **Yes, it is.**

14:36:48 Q. **And if you could turn, Doctor, to column 29, lines 37**

14:36:52 **through 40, and that's at JTX-40.16. And, again, it's**

14:37:05 **column 29, lines 37 through 40.**

14:37:18 **Do you have that, Doctor?**

14:37:19 A. **Yes, I do.**

14:37:21 Q. **And the sentence states, when tested in accordance**

14:37:23 **with the foregoing procedure, the compounds of the invention**

14:37:27 **demonstrated IC_{50}'s in the range of ten to the minus**

14:37:31 **fifth through ten to the minus tenth molar as seen in Table**

14:37:35 **I.**

14:37:35 **Do you see that?**

14:37:36 A. **Yes.**

14:37:37 Q. **And that passage indicates that those compounds of the**

14:37:42 **invention were actually administered and evaluated in an**

14:37:46 **assay; is that correct?**

14:37:47 A. **That's correct.**

14:37:49 Q. **And if you could turn to right below that passage,**

14:37:53 **Table 1. And the first entry in Table 1 is example number**
14:38:00 **14.**
14:38:00 **Do you see that?**
14:38:01 A. **Yes.**
14:38:07 Q. **And example number 14 was the example that we've just**
14:38:12 **looked at which had a Boc group connected to the N-terminus**
14:38:17 **of phenylalanine?**
14:38:19 A. **That's correct.**
14:38:20 Q. **And so in this case, the example 14 was the final**
14:38:23 **compound as it was administered for evaluation in an assay;**
14:38:29 **is that correct?**
14:38:29 A. **That's correct.**
14:38:30 Q. **So what we have here, Doctor, is an example of what is**
14:38:35 **standardly used as a protecting group in peptide synthesis,**
14:38:39 **the Boc group. Here it's used as part of the final product**
14:38:45 **and is not removed; is that correct?**
14:38:46 A. **Yes.**
14:38:47 Q. **Doctor, if you could turn to Tab 7 in your binder.**
14:38:59 A. **Tab 7?**
14:39:01 Q. **There is a Tab 7. There's 1 through 9 at the back of**
14:39:05 **your binder. These are documents that do not have an**
14:39:09 **exhibit number, a trial exhibit number.**
14:39:11 A. **Okay. Yes.**
14:39:18 Q. **And, Doctor, the article behind Tab 7 is titled,**
14:39:24 **kinetic properties of the binding of alph-lytic protease to**

14:39:28 **peptide boronic acids. Is that correct?**

14:39:31 A. **That's correct.**

14:39:31 Q. **And you are an author of this paper?**

14:39:36 A. **That's correct.**

14:39:36 Q. **Is this some of the research that you mentioned earlier in your testimony when you were describing your work in the 1980s?**

14:39:42 A. **It is.**

14:39:43 Q. **And what year was this paper published?**

14:39:46 A. **Published in 1988.**

14:39:48 Q. **And when was the final manuscript that resulted in this article submitted to the Journal of Biochemistry?**

14:39:56 A. **It looks like it was submitted on October 27, 1987.**

14:40:01 Q. **And so all of this work that is reported in your manuscript in Biochemistry was completed at least by July 7th, 1988; is that correct?**

14:40:12 A. **I would assume so, yes.**

14:40:13 Q. **If you could turn to Page 7685 of the article, and that is -- and focus your attention at Table 2.**

14:40:25 A. **Yes.**

14:40:25 Q. **Does the left side of the table identify some of the peptide boronic acids you tested as enzyme inhibitors?**

14:40:35 A. **It does.**

14:40:35 Q. **And don't the inhibitors 6, 7 and 8 contain a Boc moiety?**

14:40:41

14:40:42 A. **They do.**

14:40:43 Q. **What is Boc moiety in 6, 7 and 8 in your peptide boronic acids article?**

14:40:47

14:40:48 A. **I'm sorry. Can you repeat that?**

14:40:51 Q. **And what is Boc in the inhibitors 6, 7 and 8?**

14:40:55 A. **It's an N-terminal protecting group in this case.**

14:40:57 Q. **Pardon me?**

14:40:58 A. **It's an N-terminal protecting group.**

14:41:00 Q. **And so it is on the N terminal group of, in this case, if I look at 6, 7 and 8, alanine; is that correct?**

14:41:05

14:41:08 A. **I'm sorry. Say that again. I'm not sure I understood what you said.**

14:41:15

14:41:15 Q. **Certainly. If you would look back at Table 2.**

14:41:18 A. **Yes.**

14:41:19 Q. **And the compounds 6, 7 and 8.**

14:41:23 A. **Compounds 6, 7 and 8. Yes.**

14:41:27 Q. **And each of those compounds have a Boc group; is that correct?**

14:41:29

14:41:30 A. **They do. Yes, they do.**

14:41:32 Q. **And the Boc group is attached to the N terminal group of alanine; is that correct?**

14:41:36

14:41:38 A. **That's correct. Attached to alanine. Yes.**

14:41:41 Q. **And as we said before, as of 1989, Boc was standardly used, standard use in the synthesis of peptides and often removed in peptide synthesis; is that correct?**

14:41:45

14:41:51

14:41:54 A. **That's correct.**

14:41:55 Q. **And in this case, what we're looking at are examples of where a group that's standardly used for peptide synthesis is actually part of the final molecule; is that correct?**

14:42:05 A. **That is correct.**

14:42:07 Q. **Doctor, if you would look on that same page where Table 2 is, it's 7685 is the page. And on the right column, you are going to see a heading, stoichiometry of peptide boronic acid binding.**

Do you see that?

14:42:30 A. **Yes.**

14:42:31 Q. **And the first sentence after that subheading reads, the most -- excuse me. Strike that. The first sentence after that subheading reads, the most effective peptide boronic acid, Boc-Ala-Pro-boroVal-OH, was used to confirm that a one-to-one complex is formed with the inhibitor and protease by using the titration procedure of Morrison (1969).**

Do you see that?

14:43:05 A. **Yes, I do.**

14:43:06 Q. **So is it the case that the most effective peptide that was studied here had the Boc group on the N terminal?**

14:43:14 A. **That is the case here, yes.**

14:43:17 Q. **So doesn't your peptide boronic acid article**

14:43:21 **demonstrate the use of Boc not just as a transient group**
14:43:25 **during synthesis, but rather as use of a final compound?**
14:43:28 A. **Yes, it does.**
14:43:49 Q. **Doctor, if you would turn to Tab 6 in your binder.**
14:43:55 **Again, this is in the back. These documents are not trial**
14:44:00 **exhibits.**
14:44:11 A. **Okay.**
14:44:12 Q. **If you would turn to the first page and look at the**
14:44:16 **title, the title reads N-(Fluorenyl-9-methoxycarbonyl) amino**
14:44:22 **acids, a class of antiinflammatory agents with a different**
14:44:26 **mechanism of action.**
14:44:28 **Do you see that?**
14:44:29 A. **I do.**
14:44:29 Q. **What in the title does N-(fluorenyl-9-methoxycarbonyl)**
mean?
14:44:36 A. **That's Fmoc.**
14:44:39 Q. **Is it acceptable to you if we refer to this article as**
14:44:43 **the Fmoc amino acids article?**
14:44:46 A. **Yes, it is.**
14:44:48 Q. **If you would turn to Page 359 of the Fmoc amino acids**
14:44:56 **article. I would like to focus your attention on the first**
14:45:00 **sentence of the first paragraph under the discussion, which**
14:45:05 **will be highlighted on the screen. That sentence states, In**
14:45:10 **this report we have described antiinflammatory activities of**
14:45:14 **a series of N-(fluorenyl-9-methoxycarbonyl) amino acids.**

14:45:21 **Do you understand that, Doctor, to mean that**
14:45:24 **there are amino acids that have the Fmoc group attached?**
14:45:29 A. **Yes, I do.**
14:45:31 Q. **If we could turn to the last sentence of this first**
14:45:36 **paragraph, that states, because their actions involve**
14:45:39 **leukocyte functions, we have designated them leumedins. Do**
14:45:48 **you see?**
14:45:48 A. **Yes.**
14:45:48 Q. **Do you see that, the leumedins are a series of amino**
14:45:55 **acids containing the Fmoc group. Is that correct?**
14:45:57 A. **Yes, that's correct.**
14:45:58 Q. **If we could turn to Figure 1 of Page 356 of the Fmoc**
14:46:09 **article.**
14:46:15 **Doctor, if you would focus your attention on the**
14:46:18 **second row on the left-hand side, the first molecule there,**
14:46:22 **it's labeled NPC 15199. Do you see that?**
14:46:35 A. **Yes.**
14:46:38 Q. **Is that Fmoc attached to leucine?**
14:46:41 A. **Yes, it is.**
14:46:42 Q. **And leucine is a standard amino acid. Is that**
14:46:44 **correct?**
14:46:44 A. **That is correct.**
14:46:45 Q. **Isn't it the case that NPC 15199 consists of no other**
14:46:54 **chemical moiety except Fmoc and leucine?**
14:46:58 A. **Yes.**

14:46:58 Q. **And the Fmoc that is used on NPC 15199 is the same**
14:47:06 **chemical moiety that is used to protect an N-terminus**
14:47:08 **peptide during the peptide synthesis. Is that correct?**
14:47:13 A. **That's correct.**
14:47:13 Q. **The Fmoc of the NPC 15199 is the same Fmoc chemical**
14:47:23 **moiety that is identified as a Z group of Claim 1 of the**
14:47:28 **'7,803 patent. Correct?**
14:47:29 A. **Yes.**
14:47:29 Q. **And Fmoc is part of the final compound of NPC 15199.**
14:47:36 **Is that correct?**
14:47:36 A. **In this case, that is true.**
14:47:39 Q. **If we could turn now to Page 359, focusing on the**
14:47:45 **Subsection NPC 15199 In an enteric formulation is effective**
14:47:52 **against oxazolone.**
14:47:56 **Do you see that?**
14:47:57 A. **Yes, I do.**
14:47:58 Q. **The first sentence under that subheading states, "In**
14:48:02 **all experiments presented thus far, administration of the**
14:48:05 **N-(fluorenyl-9-methoxycarbonyl) amino acids was by an i.p.**
14:48:11 **route."**
14:48:12 A. **Yes.**
14:48:13 Q. **And that indicates that the Fmoc amino acids were**
14:48:17 **administered. Is that correct?**
14:48:19 A. **Yes.**
14:48:19 Q. **And so the Fmoc group would have been part of the**

14:48:22 **final molecule that was administered. Is that correct?**

14:48:28 A. **That's correct.**

14:48:28 Q. **If we could turn to the last part of this paragraph,**

14:48:34 **where it says, Thus, an enteric-coated bead formulation of**

14:48:39 **NPC 15199 was prepared that could be administered by feeding**

14:48:45 **tube. This formulation was tested in the oxazolone edema**

14:48:51 **model. Enteric-coated NPC 15199 was administered 30 minutes**

14:48:57 **before oxazolone, and edema was measured 24 hours later.**

14:49:02 **When in this formulation, NPC 15199 exhibited oral activity**

14:49:08 **(Table 3).**

14:49:10 **Do you see that?**

14:49:11 A. **Yes.**

14:49:11 Q. **Is it the case that this passage indicates that NPC**

14:49:16 **15199 was actually formulated in an enteric formulation and**

14:49:22 **administered?**

14:49:23 A. **Yes.**

14:49:23 Q. **Isn't it the case, Doctor, that the Fmoc article,**

14:49:29 **Doctor, demonstrates the use of Fmoc not in a situation of**

14:49:34 **solid phase peptide synthesis but actually part of the final**

14:49:42 **molecule?**

14:49:42 A. **Yes.**

14:49:42 Q. **If we could turn to JTX-25 in your binder. If you**

14:49:57 **could refer to Table 1, which is at JTX-25.2?**

14:50:05 A. **Okay.**

14:50:05 Q. **And do you understand that in Table 1 there is the**

14:50:10 **evaluation of smooth muscle activities of bradykinin analogs**
14:50:16 **with modifications in position 7?**
14:50:20 A. **Yes.**
14:50:20 Q. **Modifications that are made are only at position 7.**
14:50:29 **Is that correct?**
14:50:29 A. **I believe that's correct, yes.**
14:50:30 Q. **So in all of those cases, the only amino acid that**
14:50:34 **conferred bradykinin antagonist activity in one assay was**
14:50:39 **the D-phenylalanine. Is that correct?**
14:50:44 A. **Yes, that's correct.**
14:50:45 Q. **So isn't it the case that a number of the amino acids**
14:50:50 **listed there that did not confer bradykinin antagonist**
14:50:55 **activity when inserted into position 7 of the analog were**
14:51:00 **D-aromatic compounds?**
14:51:03 A. **Can you rephrase that question or say the question**
14:51:06 **again?**
14:51:06 Q. **Certainly. Isn't it the case in this table that a**
14:51:10 **number of the amino acids that were inserted in the**
14:51:14 **bradykinin molecule and did not convert the molecule to an**
14:51:20 **antagonist were D-aromatic amino acids?**
14:51:24 A. **I can't completely agree with your statement there.**
14:51:28 **If you look at these results you will see they were**
14:51:31 **measuring for the most part agonist activity. If you look**
14:51:35 **at the report, many of these with the D-substituted amino**
14:51:39 **acid had essentially no agonist activity. They did not set**

14:51:42 up, quantify the antagonist activity, in most cases. I
14:51:47 think in most cases the conclusion would be the substitution
14:51:51 of D-amino acid destroyed the agonist activity, which would
14:51:54 be the first step toward making an agonist. So I think any
14:51:58 one of these would still fit with the SARs taught by
14:52:03 Stewart.
14:52:03 Q. In this data set, they don't report any antagonist
14:52:09 activity but they actually did look for it, didn't they?
14:52:13 A. I am not sure exactly what they looked for. I can
14:52:16 only tell you what's in the table. What's in the table is a
14:52:21 measure of the agonist activity and the agonist activity in
14:52:24 most cases was essentially destroyed by substituting a
14:52:27 D-aromatic amino acid.
14:52:28 Q. Doctor, if you could turn down on Page 162 on the
14:52:36 left-hand side under Results and Discussion, there is a
14:52:39 second full paragraph that begins with the words single
14:52:44 substitution, it states, "Single substitution of a
14:52:47 D-aliphatic or a D-aromatic amino acid residue at position 7
14:52:53 of BK produced analogs with little or no agonist activity,
14:52:56 and no antagonist activity, in the uterus assay?"
14:53:02 A. Yes. That is the key phrase, none in the uterus
14:53:05 assay. This is one assay. And they didn't see much
14:53:10 antagonist activity in the conditions they performed that
14:53:13 assay.
14:53:13 Q. If we could just look down another paragraph further,

14:53:19 **the next full paragraph at that column begins. On the**
14:53:23 **ileum, all of the analogs listed were essentially devoid of**
14:53:28 **both agonist and antagonist activity, with one exception.**
14:53:36 **[D-Phe7]-BK produced a clear inhibition of the the action of**
14:53:39 **BK.**
14:53:40 **Isn't that reporting in both the two assays that**
14:53:44 **were evaluated the only D-aromatic amino acid substituted in**
14:53:49 **bradykinin that produced antagonist activity was D-Phe?**
14:53:56 A. **Yes. It is also the case that the D-Phe antagonist**
14:54:01 **activity was relatively modest. It was not a striking**
14:54:05 **effect. This was an early paper where they were just**
14:54:10 **deciding to find whether it was required. D-Phe is a**
14:54:12 **preferred substitution there. That was the first one that**
14:54:15 **showed up in this assay that they then pursued further and**
14:54:20 **further characterized the SAR that led to the**
14:54:27 **structure-activity relationships correlating D-aromatic**
14:54:30 **amino acids as being crucial for antagonist activity. So**
14:54:35 **yes, D-phenylalanine was the best of these that showed up in**
14:54:39 **this assay.**
14:54:39 Q. **So a person of ordinary skill in the art would**
14:54:42 **understand from this article JTX-25 that a single**
14:54:46 **substitution at position 7 of a bradykinin analog could not**
14:54:50 **necessarily confer antagonist activity, not even a**
14:54:55 **D-aromatic amino acid. Isn't that correct?**
14:54:58 A. **In this single assay. There is different assays that**

14:55:02 one could look at. In this particular assay, the rat uterus
14:55:06 test, that's correct, that some of these of these D-Phe
14:55:10 amino acid substitutions did not show striking antagonist
14:55:14 activity.
14:55:14 Q. If you could turn to Table 2 in this article, Doctor.
14:55:18 It is on JTX-25.3. It's at the top of the page. If we take
14:55:29 a look at that, isn't it the case that D-Phe 7 bradykinin is
14:55:36 being compared to another analog, Thi 5,8 D-Phe 7-BK.
14:55:43 Correct?
14:55:45 A. That's correct.
14:55:46 Q. And you will see an increase in the potency and I
14:55:54 guess the spectrum of action I would call it because now
14:55:57 what you have is activity in both the rat uterus and the
14:56:01 guinea pig ileum represented by the numbers 6.4 and 6.3.
14:56:06 Correct?
14:56:07 A. That's correct.
14:56:07 Q. That compares with a D-Phe 7-BK only bradykinin which
14:56:12 was only active in the guinea pig ileum and had a lower pA2
14:56:20 value of 5. Correct?
14:56:26 A. Where does it say those are pA2 values?
14:56:34 Q. If we could take a look at the legend below the table,
14:56:39 Doctor. You will see the second sentence in the legend says
14:56:51 antagonist potency is given at the pA2 value of Schild.
14:56:59 A. Okay.
14:56:59 Q. Isn't it the case, Doctor, that JTX-25 demonstrates to

14:57:05 a person of ordinary skill in the art that a single
14:57:09 substitution in bradykinin at Position 7 with a D-aromatic
14:57:16 acid does not necessarily confer antagonist activity but if
14:57:21 other changes are made in the molecule that could change the
14:57:26 activity?
14:57:26 A. Well, I can't agree with that entirely. A person of
14:57:30 skill in the art would look at that data and say what's
14:57:33 going on there, you will notice the D-Phe bradykinin is 36
14:57:38 percent destroyed. So what is happening is the N-terminus
14:57:42 of a bradykinin analog that only has D-Phe in it is not
14:57:49 detecting striking degradation. Because of that lack of
14:57:50 protection it sort of then does not do as well as another
14:57:53 amino acids that may have some protection.
14:57:57 As you can see, the other analog down there
14:58:01 destroyed as much because of the other substitutions it has
14:58:03 in it. This is what Dr. Stewart taught, that substituting
14:58:08 other amino acids could enhance potency by in part creating
14:58:15 analogs that would be resistant to degradation.
14:58:18 Q. So a person of ordinary skill in the art would
14:58:22 understand that the Thi 5,8 position conferred an increase
14:58:25 in metabolic stability?
14:58:27 A. That is what this table is saying. Because it is
14:58:29 indicating that there was not destruction of the bradykinin
14:58:37 analog there.
14:58:37 Q. Doctor, if we could turn to the next document, JTX-34.

14:58:50 **It's going to be another Stewart and Vavrek. Doctor, did**
14:59:03 **you consider this article in the work that you did in the**
14:59:06 **course of this litigation?**
14:59:12 A. **I believe I did, yes.**
14:59:17 Q. **So if you would turn to Table 1 of JTX-34, it actually**
14:59:24 **appears, it starts at JTX-34.5 and runs all the way over to**
14:59:30 **JTX-34.7, so it's a very long table. Just to orient you,**
14:59:38 **there is a legend at the end of the table also on JTX-34.7.**
14:59:46 A. **Okay.**
14:59:47 Q. **Doctor, if you could turn your attention, we will**
14:59:50 **highlight it on the screen, I know this is very hard to**
14:59:55 **read, I am looking at the analog Thi 5,8 D-Phe BK. Is that**
15:00:04 **the same compound that we were just discussing in JTX-25?**
15:00:09 A. **I believe it is, yes.**
15:00:10 Q. **In this paper, isn't it the case that the Thi 5,8**
15:00:16 **D-Phe 7 demonstrates significant pA2 values in both the**
15:00:21 **guinea pig and rat ileum, and also in the rat blood pressure**
15:00:28 **assay?**
15:00:29 A. **At the moment, I don't see the -- okay, the 6.5 there,**
15:00:35 **I am sorry.**
15:00:36 Q. **Maybe it would be helpful if we take you up to the top**
15:00:40 **of the table, and you can see the assays.**
15:00:44 A. **Okay. Here they are listing it as just showing**
15:00:52 **antagonist activity.**
15:00:56 Q. **If we take a look about five rows down, there is**

15:01:00 **another analog, Thi 5,8 Dh-Phe 7. Do you see that?**

15:01:06 A. **Yes.**

15:01:07 Q. **Do you understand what Dh-Phe represents in this table?**

15:01:16 A. **That must be an analog of phenylalanine, D-phenylalanine.**

15:01:21 Q. **If you could take a look at JTX34.7. It is the legend of the table. The fourth line from the bottom begins abbreviations, it says abbreviations for residues?**

15:01:38 A. **So it is a D-homophenylalanine. That means it's an analog, the chain connecting the aromatic rings to the backbone is one carbon longer.**

15:01:49 Q. **Right. Let's take a look at the data for the homophenylalanine analog.**

15:01:55 **If we could go back to Table 1, the first page of Table 1, and compare the Thi 5,8 D-Phe 7 and the Thi 5,8 D-homophenylalanine. Isn't it the case, Doctor, that the substitution of D-homophenylalinine for D-phenylalanine abolishes the bradykinin antagonist activity?**

15:02:24 A. **It does appear that's the case here, yes.**

15:02:27 Q. **Structurally, what is the difference between D-phenylalanine and D-homophenylalanine?**

15:02:34 A. **The aromatic ring is more extended. It is further away from the back.**

15:02:43 Q. **So isn't it the case that D-homophenylalanine has one**

15:02:49 more methylene group in it than phenylalanine?
15:02:54 A. That's correct. One more carbon as you stand away
15:02:59 from the backbone.
15:03:02 Q. The simple change of inserting a methylene group and
15:03:06 going from a phenylalanine to a homophenylalanine takes what
15:03:11 we know is a potent kind of bradykinin antagonist and
15:03:17 abolishes that activity. Correct?
15:03:18 A. That appears to be the case here, yes.
15:03:20 Q. If we could take a look in going to JTX-34.6, now, I
15:03:29 would like to compare two other analogs, and I would like to
15:03:34 compare the Thi -- the D-Arg Thi 5,8 D-phenylalanine with
the D-Arg Thi 5,8 D-homophenylalanine.
15:03:51 Once again, Doctor, it is the case that the
15:03:54 D-Arg Thi 5,8 D-Phe 7 is a bradykinin antagonist in all of
15:04:03 the assays tested. Correct?
15:04:05 A. Yes.
15:04:05 Q. And the single change of converting the
15:04:07 D-phenylalanine to the D-homophenylalanine, which is just
15:04:12 one methylene group again, abolishes all activity. Isn't
15:04:17 that correct?
15:04:17 A. That's the case, yes.
15:04:24 Q. Doctor, if you could turn to Tab 1 in your binder,
15:04:28 it's been labeled PDX10.1, Doctor, what I have on the screen
15:04:44 are the structures of homophenylalanine, phenylalanine, and
15:04:49 what we were talking about during your direct examination,

15:04:53 **which is the amino acid Tic. Do you see that?**

15:04:57 A. **Yes.**

15:04:59 Q. **So the difference between homophenylalanine and**

15:05:03 **phenylalanine is the one methylene group. Isn't that**

15:05:09 **correct?**

15:05:10 A. **That's correct.**

15:05:10 Q. **So that's what is different as compared to the**

15:05:13 **phenylalanine?**

15:05:14 A. **Yes.**

15:05:14 Q. **And when you go from D-phenylalanine to**

15:05:19 **D-homophenylanine in the 7 position of a bradykinin analog,**

15:05:26 **you abolish activity. Is that correct?**

15:05:28 A. **That appears to be the case.**

15:05:29 Q. **And isn't it the case that the only difference between**

15:05:35 **phenylalanine and the Tic amino acid is again one methylene.**

15:05:39 **Isn't that correct?**

15:05:41 A. **That's completely different. The methylene group is a**

15:05:45 **completely different substitution and would have a**

15:05:47 **completely different effect on a person of skill in the art**

15:05:50 **looking at a structure-activity at this point. In one case,**

15:05:54 **that is contained within the normal bounds of the analogs**

15:05:56 **you are looking at. Whereas in the other case you are now**

15:05:59 **extending the aromatic ring out beyond where it had been**

15:06:02 **extended before.**

15:06:04 **So it won't be fair to say they both have just**

15:06:09 **one more methylene group.**

15:06:11 **Q. In fact, the Tic molecule has the one methylene group,**
15:06:15 **but now you have completely changed the structure, you have**
15:06:18 **made it a conformationally constrained amino acid?**

15:06:23 **A. But that conformationally constrained amino acid**
15:06:23 **overlays closely nevertheless with phenylalanine and does**
15:06:29 **not extend beyond the boundary that phenylalanine would**
15:06:31 **normally occupy.**

15:06:32 **Q. What we have in front of us, the actual data we have**
15:06:35 **in front of us, Doctor, is taking a molecule where you only**
15:06:39 **change it by one methylene group and you can see other**
15:06:43 **substitutions in the analog as well, what that does is it**
15:06:46 **completely abolishes the activity when you go from**
15:06:49 **phenylalanine to homophenylalanine. We have actual data to**
15:06:53 **show that and support that. We don't have, unless you can**
15:06:57 **show me or tell me now, we have not seen any data about how**
15:07:02 **going from phenylalanine to the Tic molecule in the 7**
15:07:06 **position would impact bradykinin activity?**

15:07:12 **A. I can only say that a person of skill in the art would**
15:07:15 **view the difference between phenylalanine and Tic as more**
15:07:19 **structured, similar to each other, than homophenylalanine is**
15:07:22 **to phenylalanine because of that extra methylene group**
15:07:25 **extending it farther out into space.**

15:07:36 **Q. Isn't it the case, Doctor, that in this litigation,**
15:07:43 **there has been no identification of the use of Tic in any**

15:07:48 **bradykinin analog? Is that correct?**

15:07:50 A. **Not outside the patents at issue here.**

15:07:54 Q. **That's correct. So there has not been any identification of Tic in bradykinin antagonist literature prior to January 1989. Right?**

15:08:05 A. **That's correct.**

15:08:05 Q. **And there hasn't been any identification of the use of a conformationally constrained bicyclic analog like D-Tic in position 7 prior to January 1989. Isn't that correct?**

15:08:25 A. **I am not entirely sure that's correct. I would have to go back and take a look at the literature.**

15:08:32 Q. **We haven't seen one today, have we, Doctor?**

15:08:35 A. **We have not seen one today.**

15:08:37 Q. **So ultimately, what we have is data that demonstrates the abolishment of bradykinin antagonist activity where you simply take and insert one methylene group from the phenylalanine to homophenylalanine, we have no information going from D-phenylalanine to D-Tic, we have no information about conformationally constrained amino acids in a bicyclic system in position 7. Isn't that correct?**

15:09:11 A. **There is no information that we have seen today on the effect of Tic being substituted other than those patents that are at issue.**

15:09:22 Q. **And those patents that are at issue, there is nothing in the prior art that gives you any guidance really as to**

15:09:30 **how Tic, inserted at -- D-Tic inserted at position 7 is**
15:09:35 **going to affect the potency of a bradykinin antagonist. Do**
15:09:40 **we?**
15:09:40 A. **I would not agree there is no guidance in the**
15:09:43 **literature that for a person of skill in the art to make a**
15:09:50 **reasonable expectation of what would happen with the Tic**
15:09:52 **substitution. So I cannot agree with the statement as is.**
15:09:55 Q. **We don't have any information from the prior art as to**
15:09:58 **how the insertion of D-Tic into a bradykinin analog would**
15:10:04 **impact the metabolic stability of the analog, do we?**
15:10:10 A. **We don't have a direct showing of what happens if you**
15:10:13 **make that substitution. But a person of skill in the art**
15:10:16 **would have a reasonable expectation that a D-Tic**
15:10:19 **substitution would decrease proteolysis for the simple**
15:10:24 **reason that it is a non-naturally occurring amino acid of**
15:10:27 **the D configuration and that it is a proline-like amino acid**
15:10:34 **that is in that range for further resistance.**
15:10:36 **So the person of skill in the art would have a**
reasonable expectation that D-Tic would confer resistance of
15:10:45 **proteolysis.**
15:10:45 Q. **Isn't it the case, Doctor, that not just in the**
15:10:50 **bradykinin literature prior art but we have identified no**
15:10:54 **prior art in this case that demonstrates how D-Tic changes**
15:11:00 **the metabolic stability of a compound when it is inserted**
15:11:06 **into a peptide?**

15:11:09 A. **There is no information specifically related to details in the prior art related to D-Tic other than the patents that are issued today.**

15:11:11 Q. **The patents aren't prior art. Is that the case?**

15:11:13 A. **I guess, yes.**

15:11:16 Q. **Doctor, if we could turn to JTX-1, that is the '333 patent in suit here today. If you will turn to JTX-1.24. If we could go to Claim 14. And Claim 14 is at Column 44. It is at Line 45.**

15:11:20 A. **Okay.**

15:12:04 Q. **So a person of ordinary skill in the art, just looking at the structure of Claim 1, would they know if it had biological activity?**

15:12:12 A. **A person of skill in the art by what's in the prior art would have a reasonable expectation that that peptide would be a bradykinin antagonist.**

15:12:30 Q. **So the way that a person of ordinary skill in the art would understand that it has activity would have to be through the prior art. Is that correct?**

15:12:30 A. **That is correct.**

15:12:35 Q. **If we could go to your demonstrative, Doctor, at DDX2-38. If we could bring that up, Doctor, I have your demonstrative on the screen. Looking at Table 2. We talked about the D-Arg Thi 5,8 D-Phe 7 compared to D-Arg Thi 5,8 D-homophenylalanine. So we compared a compound that had**

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15:14:00 **D-phenylalanine here at position 7 and D-homophenylalanine**
15:14:06 **at that position. So those two molecules also had D-Arg at**
15:14:12 **the zero, that would confer enzymatic resistance, they also**
15:14:17 **had Thi -- both had Thi-5 and Thi-8, which alteration**
15:14:23 **enhances potency. So isn't it the case, Doctor, that there**
15:14:26 **would be nothing more that a person of ordinary skill in the**
15:14:29 **art would know what to do with those molecules except**
15:14:33 **looking at the fact that D-homophenylalanine here abolishes**
15:14:39 **activity, D-phenylalanine keeps activity, a person of skill**
15:14:44 **in the art would understand there is no other place that you**
15:14:49 **could change this molecule based on what Stewart and Vavrek**
15:14:53 **taught to change that agonist -- or to change the, abolish**
15:15:00 **activity and make it an antagonist. Could you?**
15:15:04 **THE COURT: Do you understand that question,**
15:15:08 **Doctor?**
15:15:08 **THE WITNESS: I do.**
15:15:10 **A person skilled in the art, confronted with the**
15:15:13 **fact that D-homophenylalanine abolishes the activity of this**
15:15:16 **agonist peptide, in the context of the other changes, would**
15:15:20 **tell him that that homophenylalanine exceeded the boundaries**
15:15:25 **of what can be accommodated by binding to the bradykinin**
15:15:29 **receptors, and therefore would probably make a note that**
15:15:31 **being too far away is not a good thing and they would**
15:15:34 **confine themselves to antagonists that stayed within the**
15:15:38 **confines of a phenylalanine ring structure, not extended**

15:15:43 **beyond.**

15:15:43 **I haven't seen the data. The first thing I want**

15:15:46 **to know about the homophenylalanine is does it have**

15:15:50 **bradykinin receptor binding potency or does it not bind any**

15:15:54 **longer to the receptor because having that longer group**

15:15:57 **could very well block binding completely, the bradykinin**

15:16:01 **receptor that can only be so long and no longer, at which**

15:16:05 **point you abolish the activity.**

15:16:07 Q. **Really what a person of ordinary skill in the art**

15:16:10 **would only have in the prior art the information that we**

15:16:14 **took out of JTX-34, they would have nothing else, would**

15:16:19 **they?**

15:16:19 A. **I am not sure I understand that at all. We would only**

15:16:23 **have what we took from JTX-34?**

15:16:27 Q. **Yes. The head-to-head comparison, if you are looking**

15:16:31 **for data that would demonstrate how to understand the**

15:16:33 **change, you have head-to-head data in the D-Arg Thi 5,8**

15:16:41 **D-phenylalanine versus D-Arg Thi 5,8 D-homophenylalanine,**

15:16:44 **other than that, a person of ordinary skill in the art could**

15:16:47 **only speculate as to what something like D-Tic would do if**

15:16:52 **inserted in that molecule. Isn't that the case?**

15:16:55 A. **I don't believe I can agree with that, the**

15:16:58 **D-phenylalanine data is not the only thing a person would**

15:17:04 **have to go on in this case. We have lots of other prior art**

15:17:08 **that indicates there are substitutions that work, and there**

15:17:11 are a variety of substitutions that work in that position. These substitutions we are talking about have the attributes of the ones we know that will work.

Q. I guess what we don't have is data that are a head-to-head comparison as I have shown you?

A. We are saying would a person of skill in the art have a reasonable expectation with the data that's out there. The reasonable expectation would be that that substitution would work.

Q. Doctor, talking about now Position 8. Let's call up Claim 14 of the '333 patent. Again, that's JTX-1. I believe it's at Column 44.

Position 8 of Claim 14 of the '333 patent, Doctor, is conformationally constrained by the amino acid moiety Oic. Isn't that correct?

A. That's correct.

Q. And isn't it the case that prior to January 1989, there was no prior art that demonstrated the use of Oic in the bradykinin analog? Correct?

A. That's true, yes.

Q. Isn't it the case that as of January 1989 there was no prior art that demonstrated how the insertion of Oic into any peptide impacted its metabolic stability?

A. I am not entirely sure about that. I would have to go back and look at that to see if the data is available, to

have the ability to tell us that.

Q. So we haven't seen today, Doctor, isn't it the case, we haven't seen today any information as to how the insertion of Oic into a peptide impacts its metabolic stability. Isn't that the case?

A. I think that's true.

THE COURT: Counsel, how much more do you have?

MS. KUZMICH: I might have about 15 more minutes, Your Honor.

THE COURT: Let's take a stretch.

15:34:20 (Recess taken.)

15:34:20 THE COURT: Please, take your seats.

15:34:22 BY MS. KUZMICH:

15:34:23 Q. There. Are you okay to continue?

15:34:25 A. Yes, I am. I am fine.

15:34:34 Q. Good.

15:34:35 If we could turn to DTX-114 in your binder. It is the article that everyone has been referring to as

15:34:39 Spragg. Doctor, I believe you referred to Spragg in your

15:34:42 direct examination. Is that correct?

15:35:17 A. Yes, I did.

15:35:18 Q. Doctor, for what purpose are you relying on Spragg?

15:35:19 A. So Spragg reports biological activity of some prior

15:35:38 art antagonists, showing the sequences of the modified

15:35:49 bradykinin sequences that have efficacious activity. I am

15:35:55

15:36:03 not sure, for all the reasons I described earlier, it shows
15:36:10 antagonist studies of bradykinin analogs. It's also for the
15:36:20 preference of L-Arginine over lysine.
15:36:30 Q. Doctor -- also, this one refers to --
15:36:34 A. I remember now. They have a different numbering
15:36:36 system. The P2, this is where the cyclohexyalanine was
15:36:42 shown to be accommodated in the 8 position.
15:36:48 Q. And that cyclohexyalanine in the 8 position, was that
15:36:54 for the specificity, the Position 8 of a bradykinin
15:37:00 antagonist, or was it for human urinary kallikrein?
15:37:07 A. We were using this to indicate that cyclohexylalanine
15:37:12 was a proline analog, that proline was shown to work in the
15:37:18 context of a bradykinin antagonist peptide.
15:37:23 Q. Doctor, if you could turn to the first page of
15:37:29 DTX-114. On the right column, the paragraph above Method,
15:37:35 there is a statement, I will read that, "In the course of
15:37:39 studies to identify features important for the design of
15:37:43 specific substrate sequence analog inhibitors" --
15:37:48 THE COURT: Where are you reading from, counsel?
15:37:54 MS. KUZMICH: We are on DTX-114, Page 5, on the
15:37:57 right-hand column, Your Honor.
15:37:59 THE COURT: Go ahead. Are you there, Doctor?
15:38:01 THE WITNESS: Yes.
15:38:03 BY MS. KUZMICH:
15:38:03 Q. "In the course of studies to identify features

15:38:06 **important for the design of specific substrate sequence**
15:38:09 **analog inhibitors of glandular kallikreins, Reference 21, it**
15:38:16 **became apparent that some of these features are shared by**
15:38:19 **bradykinin analog antagonists, Reference 27. These include**
15:38:24 **a preference for L-Arginine over L-Lysine at P1 and for**
15:38:30 **bulky D-amino acids at P3."**
15:38:38 **Doctor, before I read this statement, you**
15:38:42 **referred to the positions in the Spragg article and you**
15:38:46 **referred to position P2 as 8. Is that correct?**
15:38:49 A. **That's correct.**
15:38:50 Q. **So what would position P1 be?**
15:38:54 A. **P1 would correspond to, in this case, 9.**
15:39:00 Q. **And the P3, Doctor?**
15:39:02 A. **P3 would be 7.**
15:39:04 Q. **And so the statement that I just read aloud, it talks**
15:39:09 **about the features that are shared by the analog inhibitors**
15:39:16 **of glandular kallikreins with bradykinin analog antagonists.**
15:39:19 **Is that correct?**
15:39:19 A. **Yes.**
15:39:20 Q. **And there is no mention of P2. Is that correct?**
15:39:25 A. **Not in the paragraph you read.**
15:39:30 Q. **The reference, there is a reference that talks about**
15:39:36 **the specific substrate analog inhibitor of glandular**
15:39:38 **kallikreins, Reference 21. Do you see that?**
15:39:49 A. **Yes.**

15:39:49 Q. **Did you consider Reference 21 in the course of your**
15:39:52 **work in this litigation?**
15:39:53 A. **I probably looked at Reference 21, but it was not a**
15:39:57 **key reference for forming my opinion.**
15:39:59 Q. **Well, that Reference 21, if you actually turn to the**
15:40:03 **end of DTX-114, the last page of DTX-114, which is Page 8,**
15:40:12 **you will see the Reference 21, which is Okunishi, et al.,**
15:40:16 **the design of substrate analogue tissue kallikrein**
15:40:20 **inhibitors. Do you see that?**
15:40:26 A. **Yes.**
15:40:26 Q. **If you look at Tab 9 in your binder, you will find the**
15:40:32 **Okunishi reference?**
15:40:37 A. **Yes.**
15:40:39 Q. **Doctor, have you seen the Okunishi reference before?**
15:40:55 A. **I am not sure that I have in preparation for this**
15:41:01 **issue. I think I am familiar with this paper from many**
15:41:05 **years ago. But I don't think I have looked at it recently.**
15:41:08 Q. **So I will represent that the paper concerns the design**
15:41:13 **of substrate analog tissue kallikrein inhibitors just as the**
15:41:17 **title represents.**
15:41:18 A. **Yes.**
15:41:18 Q. **If you could turn to Page 1-117 of the Okunishi**
15:41:28 **reference?**
15:41:29 A. **Yes.**
15:41:31 Q. **It is right above the discussion section, the last**

15:41:36 line. It says, "Steric restraints are not observed at S2,
15:41:44 whereas S1 invariably binds an arginyl residue more
15:41:48 efficiently than a lysyl residue."
15:41:52 Do you see that?
15:41:52 A. Yes, I do.
15:41:53 Q. Do you have an understanding of what is meant by S2
15:41:56 and S1?
15:41:58 A. Those are referring to the substrate -- what we talk
15:42:01 about, they are talking about an enzyme here. This is a
15:42:04 tissue kallikrein. The enzymes have what's referred to as
15:42:11 specificity subsites. Those are designated with this S
15:42:13 nomenclature. So S1, S2 refers to the subsites to the left
15:42:19 of the cleavage site. If you went to the right of the
15:42:22 cleavage site, those would be designated S1-prime, S2-prime,
15:42:26 and so on.
15:42:26 Q. If you could turn to Page 1-118, which is the last
15:42:33 page of Okunishi. The first full sentence there, we have
15:42:38 that highlighted on the screen, The S2 subsite is large and
15:42:43 can accommodate side chains at least as bulky as a
15:42:48 cyclohexyl group.
15:42:49 Do you see that?
15:42:50 A. Yes.
15:42:50 Q. Doesn't that suggest that human glandular kallikrein
15:42:54 can accommodate side chains at least as bulky as the
15:42:59 cyclohexyl group?

15:43:00 A. **That's what it says.**

15:43:01 Q. **It makes no mention of bradykinin antagonists, does it?**

15:43:05 A. **No, it doesn't.**

15:43:06 Q. **If we could then, I have on the screen a comparison of the statements in Okunishi to the statements in Spragg, I will read them out for you, Doctor.**

15:43:09 **On the left-hand side of the screen are the two statements that I read into the record about the Okunishi -- coming from the Okunishi reference and talking about human glandular kallikreins. "Steric restraints are not observed at S2, and the S2 substrate is large and can accommodate side chains at least as bulky as a cyclohexyl group."**

15:43:54 **From Spragg we have on the top right at DTX-114, Page 5, we have, "There is minimal steric restriction at P2."**

15:44:08 **Then below we have from Spragg the statement, "Substitution at the P2 position with bulky analogs such as cyclohexylalanine indicates that minimal steric restraints are observed at this position."**

15:44:25 **And that is from Spragg at 114, Page 7.**

15:44:30 **Isn't it the case that the language we see in Spragg talking about the P2 position and minimal steric restriction is only referring to the human kallikrein, the human glandular kallikrein and not bradykinin antagonists?**

15:44:49 A. **Yes. But they pointed out there was an overlap in what was accommodated in human kallikrein versus what was accommodated in the bradykinin receptor.**

15:44:59 **The reason for that actually is there is quite a considerable amount of crosstalk between the kallikreins and the bradykinin receptors. So they are not that dissimilar.**

15:45:13 Q. **But it is actually the case that DTX-114, Spragg, when it is talking about the overlap, it is talking about the overlap at P1 and P3, not P2. Isn't that correct?**

15:45:25 A. **I am not sure I understand that question.**

15:45:27 Q. **Let me refer you back to the first page of Spragg and the statement I read. It's DTX-114, Page 5. It's a bit confusing. Page 5 is actually the first page of the text.**

15:45:58 **It says, When they have looked at the studies to identify features important for the design of substrates for glandular kallikreins, there was a comparison and they note shared features, and here on the reference that we have they are talking about P1 and P3, not P2. Is that correct?**

15:46:22 A. **P2 is also mentioned in the Spragg article. If you look at the top of Page 205, it specifically discusses substitutions at the P2 position with bulky analogs.**

15:46:38 Q. **What it doesn't tell us there, it doesn't talk about the overlap between features in the human glandular kallikreins and bradykinin antagonists, those are just bradykinin antagonists used in these assays. Isn't that**

15:46:53 correct?
15:46:54 A. I am not sure I understand the question. What is the
15:46:59 question that you are asking exactly?
15:47:02 Q. Is Spragg, DTX-114, discussing the overlap of features
15:47:09 between bradykinin antagonists and human glandular
15:47:14 kallikreins at the P2 position?
15:47:16 A. Yes.
15:47:16 Q. And where is your support for that, Doctor?
15:47:22 A. The title of the paper is The Inhibition of Glandular
15:47:28 Kallikrein by Peptide Analog Antagonists of Bradykinin.
15:47:31 Q. I am specifically asking you, where is your support
15:47:33 for the proposition that the P2 position, there are shared
15:47:39 features in the P2 position between human glandular
15:47:44 kallikreins and bradykinin antagonists?
15:47:50 A. If you look at the top of Page 205, it says
15:47:54 substitutions at the P2 position, bulky analogues such as
15:47:58 cyclohexylalanine indicates that minimum steric restraints
15:48:01 are observed.
15:48:02 If you look at the table, the P2 position
15:48:05 corresponds to the 8 position of the bradykinin antagonist.
15:48:12 Q. Isn't it the case, Doctor, that that paragraph is
15:48:17 actually referring to Reference 21 that I read, the Okunishi
15:48:24 reference? If you look at the bottom of Page 114, DTX-114.7
15:48:31 on the left-hand side, Reference 21 is what is referenced,
15:48:35 and that is the kallikrein article, and that is what is

15:48:40 referring to the P2 position for the statement that you read
15:48:43 in. Isn't it?
15:48:48 A. So you are saying that on 205, the statement
15:48:51 substitution at the P2 position of bulky analogs such as
15:48:55 cyclohexylalanine is dependent on the Reference 21?
15:49:03 Q. Yes, I am, because I don't see anything referring to
15:49:07 the bradykinin antagonist requirement there.
15:49:11 THE COURT: Is that a question?
15:49:15 BY MS. KUZMICH:
15:49:15 Q. Do you see, Doctor, any reference to bradykinin
15:49:22 antagonists in there?
15:49:22 A. I also don't see a reference to Reference 21 there.
15:49:27 Q. Just --
15:49:29 A. I mean, that still is exactly the case, though. They
15:49:34 are talking about there being a similarity in the binding
15:49:38 sites of kallikrein with the bradykinin receptor. They are
15:49:41 talking about the bradykinin receptor kallikrein, they are
15:49:44 saying there is overlap or similarity. They are defining
15:49:47 what the similarities are. They are saying -- that is why
15:49:50 this nomenclature is different.
15:49:53 P2 in this case is the residue that would bind
15:49:55 to an enzyme S2 site. In our case S is 8 that corresponds
15:50:01 to the receptor site. We don't normally number receptor
15:50:06 sites the same way. So the P2 site refers to the site in
15:50:10 the kallikrein. And they are looking at bradykinin

15:50:15 antagonists that seem to bind there and seem to have a
15:50:20 similar structure-activity relationship in binding to
15:50:21 kallikrein that they do to binding to the bradykinin
15:50:28 receptor.
15:50:28 Q. Your support for your position is what you read at the
15:50:32 top of DTX-114.7. Isn't that correct? On the right-hand
15:50:36 side?
15:50:37 A. Well, to say that the P2 position will accommodate
15:50:42 bulky analogs like cyclohexylalanine, right. And
15:50:47 cyclohexylalanine, that is not the entire support for that
15:50:51 substitution. Part of that support comes from the idea that
15:50:54 cyclohexylalanine is a proline analog and proline analogs
15:50:57 are demonstrated to work in the 8 position of bradykinin.
15:51:00 So the combination of the proline analogs work.
15:51:05 Cyclohexylalanine works as a proline analog and
15:51:07 cyclohexylalanine works against kallikrein, it all fits with
15:51:12 what a person of skill in the art would have the expectation
15:51:15 that it would work in the bradykinin.
15:51:20 Q. Doctor, could we turn to the Blankley reference,
15:51:27 DTX-58. I believe you mentioned the Blankley reference this
15:51:31 morning in the direct examination?
15:51:33 A. Yes, I did.
15:51:34 Q. Doctor, if you would turn to DTX-58, Page 2, at the
15:51:46 top of the page, on the left-hand side, at the very top,
15:51:53 there is a reference to an enhanced lipophilic environment.

15:51:57 **Do you see that?**

15:52:03 A. **Yes. Okay.**

15:52:04 Q. **Does an enhanced lipophilic environment within a peptide provide any benefits to the peptide?**

15:52:15 A. **Well, it depends on what benefit you are looking for. It would provide the enhanced benefits if you wanted that portion of the peptide to interact with a lipophilic site, either on a target receptor enzyme or a tissue in the body.**

15:52:38 Q. **Is it the case that a more lipophilic peptide could have more potential benefits on the in-vivo stability of the peptide?**

15:52:47 A. **Well, you are asking if lipophilicity contributes to improved in-vivo stability. Lipophilicity all by itself might or might not. You would have to look at the context of what you were talking about.**

15:53:06 Q. **Could a more lipophilic peptide have potential benefits as to the duration of action of the peptide at the receptor?**

15:53:15 A. **Again, it depends on the context, what molecule you were talking about and for what purpose, and what is the benefit. Is it the length of the survival in the bloodstream? Is it prevention of clearance? Is it the resistance of proteolysis? You would have to know a lot more to make a reasonable prediction based on all these things.**

15:53:41 Q. **When you were referring to Blankley this morning, which is DTX-58, it was in the context of Oic. Is that correct?**

15:53:51 A. **That's correct.**

15:53:51 Q. **Isn't it the case that Blankley is silent as to how replacement of Pro with Oic impacts the metabolic stability of the peptide?**

15:54:03 A. **Yes. He didn't say that it impacted the peptide. Didn't say anything about that.**

15:54:07 Q. **Blankley, which is DTX-58, does not include any information on bradykinin antagonists. Correct?**

15:54:08 A. **Correct.**

15:54:19 Q. **Doctor, if you would turn to JTX-28 in your binder. If you would go to Columns 15 and 16, it is at JTX-28.9. It spans the two columns. The table that I am going to refer you to starts at the bottom of Column 15. It continues to Column 16. Do you see that?**

15:54:24 A. **Yes, I do.**

15:54:37 Q. **So isn't it the case that you have replacement -- the third entry in that table, which is at Column 15, the very last entry, D-Arg to BK. Do you see that?**

15:54:45 A. **Yes.**

15:54:48 Q. **They are looking at in this table the percent destruction of bradykinin. Is that correct?**

15:54:53 A. **Yes.**

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15:55:23 Q. **And so compared to bradykinin, which is 98 percent**
15:55:31 **destroyed in this table, adding the D-Arg only benefits by a**
15:55:38 **very small percent, six percent. Right?**
15:55:42 A. **Yes.**
15:55:42 Q. **So it isn't as straightforward to say that if one**
15:55:48 **inserts D-Arg at the N-terminus of bradykinins, that will**
15:55:55 **enhance the metabolic stability of the peptide. Isn't that**
correct?
15:55:59 A. **Well, that is an incorrect way of looking at that.**
15:56:02 **The D-Arginine at the N-terminus would provide resistance to**
15:56:08 **aminopeptidase degradation, which is one of several ways**
15:56:09 **that that peptide can be created. We know that bradykinin**
15:56:12 **is degraded by several other enzymes towards the C-terminus**
15:56:14 **that make clips in those lines between 5 and 6, 6 and 7, and**
15:56:21 **if you block those degradations, then the D-Arg will make**
15:56:25 **all the difference in the world to the remaining stability.**
15:56:28 Q. **So it's not just one simple substitution, is it?**
15:56:32 A. **There is more than one enzyme that degrades the**
15:56:34 **peptide. To get complete stability or to get significant**
15:56:39 **stability, you would need to block all of those mechanisms**
15:56:46 **of degrading the peptide. So D-Arginine is one. It would**
15:56:51 **block the amino terminal degradation that is abbreviated by**
15:56:57 **aminopeptidases. And you can see that little bit of**
15:57:00 **difference there is reflecting probably the contribution of**
15:57:04 **aminopeptidase in the context of being chewed up by the**

15:57:06 other enzymes.

15:57:06 And in this case, in this assay, it may well be

15:57:09 that these other enzymes are present in quite high amounts,

15:57:15 and you see a very small effect of blocking the

aminopeptidase.

15:57:19 Q. So it is really unpredictable if you add the

15:57:22 D-Arginine to the N-terminus of the peptide how it is going

15:57:24 to behave?

15:57:24 Q. No. It is perfectly predictable, it is going to block

15:57:30 the aminopeptidase degradation. What is left is how much

15:57:32 other degradation will you be faced with.

15:57:34 Q. And that is unpredictable, isn't it?

15:57:36 A. No, that is kind of predictable, too.

15:57:39 Q. Doctor, when you were finishing up your direct

15:57:43 testimony, you discussed some of the comparisons of the

15:57:50 formulation of HOE 140, which is icatibant, and a prior art

15:58:00 Stewart compound. Is that correct?

15:58:01 A. That's correct.

15:58:01 Q. Did you make any comparisons as to how those two

15:58:05 peptides compared with regard to the bioavailability?

15:58:13 A. No, we did not.

15:58:13 Q. Did you make any comparisons between those two

15:58:18 molecules with respect to the time it took to reach C-max,

15:58:24 which is T-max?

15:58:25 A. I did not look at the C-max values, no.

15:58:29 Q. **So you can't speak to how active those formulations of**
15:58:37 **each of those peptides were administered, what the**
15:58:41 **pharmacokinetics of each of those peptides looks like, can**
15:58:45 **you?**
15:58:46 A. **The pharmacokinetics were not reported in those**
15:58:48 **papers.**
15:58:48 Q. **You don't know that they are, do you?**
15:58:51 A. **At the moment I could not tell you what the C-max**
15:58:54 **values are for those two peptides.**
15:58:56 Q. **Doctor, could you turn now back to DTX-59, the '7,803**
15:59:03 **patent. Turn to Claim 1. If we could have Claim 1 on the**
15:59:08 **screen.**
15:59:23 **Doctor, we looked at Claim 1 in your direct**
15:59:25 **examination and we want to look at it some more. Just a few**
15:59:28 **more questions.**
15:59:29 **If you look at the component A, A has the option**
15:59:33 **for being a bond. Right?**
15:59:36 A. **Yes.**
15:59:36 Q. **So that means that A is not a chemical moiety.**
15:59:39 **Correct?**
15:59:40 A. **Yes.**
15:59:41 Q. **And P also has the option for being a direct linkage,**
15:59:48 **which I think you said in your direct testimony was the same**
15:59:52 **thing as a bond?**
15:59:53 A. **That's correct.**

15:59:54 Q. **So P has the option of being no chemical moiety. Nothing. Is that correct?**

15:59:59 A. **That's correct.**

16:00:00 Q. **And being nothing is not an option for Z. Is that correct?**

16:00:06 A. **That is correct.**

16:00:07 **MS. KUZMICH: Your Honor, I have no more questions for Dr. Bachovchin.**

16:00:09 **THE COURT: Redirect?**

16:00:10 **MR. JAMES: Just a few questions, Your Honor.**

REDIRECT EXAMINATION

BY MR. JAMES:

16:00:13 Q. **Would you put up JTX-15 at Page 31, please?**

16:00:24 **Doctor, do you recall counsel asking you some questions about this passage of the Bodanszky paper or the Bodanszky book?**

16:00:25 A. **Yes, I do.**

16:00:42 Q. **Let's look at the bottom paragraph, if you could pull that out, Mr. Chase.**

16:00:44 **You were asked some questions about acetylation and benzoylation of amino groups being impractical. Do you recall that?**

16:00:48 A. **Yes.**

16:00:49 Q. **Acetylation and benzoylation, that refers to adding an acetyl group or a benzoyl group to a peptide. Right?**

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16:01:12 A. **Yes.**

16:01:12 Q. **And Fmoc is neither an acetyl nor a benzoyl. Right?**

16:01:17 A. **That's correct.**

16:01:18 Q. **If we could pull up DDX-57.**

16:01:28 **You were asked some questions about side chain protections. Do you recall that?**

16:01:31

16:01:32 A. **Yes, I do.**

16:01:33 Q. **And on this particular demonstrative, you are not showing any side chain protections. Right?**

16:01:37

16:01:40 A. **That's correct.**

16:01:40 Q. **So if you have Fmoc-icatibant, which is shown at the top, and no side chain protections, would it be obvious to remove the Fmoc-icabitant**

16:01:46

16:01:50

16:01:52 A. **Yes.**

16:01:34 Q. **If you have -- if a POSA had Fmoc-icatibant, no side chain protection, and it was not attached to the resin, could a person of skill in the art remove the Fmoc?**

16:01:42

16:01:46

16:01:49 A. **Yes, he could.**

16:01:50 Q. **Would the piperidine still work to remove it?**

16:01:54 A. **Yes, it would.**

16:01:55 Q. **Do you recall you were asked some questions about boronic acid peptides?**

16:01:57

16:01:59 A. **Yes.**

16:02:00 Q. **And you were asked some questions about leumedins?**

16:02:03 A. **Yes.**

16:02:04 Q. **And they had Fmoc and Boc left on them?**

16:02:07 A. **Yes.**

16:02:08 Q. **Now, neither of those compounds is the same as a bradykinin kind of analog?**

16:02:16 A. **No, they are not.**

16:02:21 Q. **Do any of those structures that you were asked about that had the Boc and the Fmoc left on them cause you to change your opinion about the obviousness of removing Fmoc from a bradykinin antagonist?**

16:02:34 A. **Absolutely not.**

16:02:35 Q. **Given what a person of skill in the art knew about a bradykinin antagonist, would a person of skill in the art have thought you should leave the Fmoc on a bradykinin antagonist in 1989?**

16:02:47 A. **No.**

16:02:49 **MR. JAMES: I have no further questions, your Honor.**

16:02:51 **THE COURT: Doctor, please be careful stepping down.**

16:02:52 **THE WITNESS: Okay. I will. Thank you.**

16:02:53 **THE COURT: Okay. Thank you.**

16:02:54 **(Witness excused.)**

16:02:55 **MR. WIESEN: Your Honor, our next witness will be Dr. Ronald Burch.**

16:03:38 **THE COURT: Okay. We are going to 5:00, Mr.**

16:03:40

16:03:42

16:03:48 **Wiesen.**

16:03:48 **MR. WIESEN: Okay. Understood, your Honor.**

16:03:50 **Dr. Burch?**

16:03:54 **Dr. Burch is a fact witness, your Honor, although a doctor.**

16:03:56

16:03:58 **THE COURT: All right.**

16:03:59 **... DR. RONALD M. BURCH, having been duly sworn as a witness, was examined and testified as follows ...**

16:04:19

16:04:21

16:04:25 **THE COURT: Good Afternoon, Doctor. Let's not have a repeat episode, please.**

16:04:27

16:04:30 **MR. WIESEN: We've agreed to exclude the fact witnesses, so he may not have seen the incident.**

16:04:32

16:04:35 **THE COURT: There's very little space to your left. Our last witness took a tumble.**

16:04:40

16:04:43 **THE WITNESS: Okay.**

16:04:48 **MR. WIESEN: We'll distribute binders, your Honor. And, your Honor, there are exhibits only, no slides.**

16:04:50

16:04:54

16:04:54 **THE COURT: Okay.**

16:04:57 **DIRECT EXAMINATION**

16:04:58 **BY MR. WIESEN:**

16:05:03 Q. **Good afternoon.**

16:05:04 A. **Good afternoon.**

16:05:05 Q. **Where do you live, Dr. Burch?**

16:05:07 A. **Live at 433 west Morris Road in Morris, Connecticut.**

16:05:11 Q. **Where do you work?**

16:05:12 A. **I work at Sanguistat, Incorporated.**

16:05:14 Q. **You're appearing here voluntarily?**

16:05:17 A. **I am.**

16:05:17 Q. **Are we paying your standard consulting rate for your time?**

16:05:20 A. **You are.**

16:05:21 Q. **If you turn in the binder to PTX-230, do you recognize that?**

16:05:27 A. **Yes. That's a copy of my curriculum vitae.**

16:05:33 **MR. WIESEN: And, your Honor, we've had an objection from the plaintiffs about entering the CV of a non-expert, so we'll just leave it as a demonstrative.**

16:05:42 **THE COURT: Okay.**

16:05:43 **BY MR. WIESEN:**

16:05:43 Q. **Did you prepare this, sir?**

16:05:45 A. **I did.**

16:05:45 Q. **If you need to refer to it, feel free. Dr. Burch, we're going to go over your entire background in a minute.**

16:05:52 **First, can you just tell the Court where you worked from 1987 until the fall of 1991?**

16:05:57 A. **From 1987 to 1991, I worked at Nova Pharmaceutical Corporation in Baltimore, Maryland.**

16:06:06 Q. **And for your testimony today, are we going to focus on**

16:06:08 **one project you worked on while at Nova?**

16:06:10 A. **Yes.**

16:06:11 Q. **What project was that?**

16:06:12 A. **That was the bradykinin antagonist project.**

16:06:15 Q. **What work did you and Nova do on bradykinin antagonists during that time period?**

16:06:20 A. **We were developing bradykinin antagonists with the intention of taking them to the clinic and ultimate commercialization.**

16:06:28 Q. **As a pharmaceutical product?**

16:06:30 A. **As pharmaceutical product, yes.**

16:06:32 Q. **Thank you.**

16:06:33 **Let's tack up a little bit. Could you just tell the Court where you did your undergraduate studies?**

16:06:39 A. **At College of Charleston in Charleston, South Carolina.**

16:06:44 Q. **What degree did you receive?**

16:06:46 A. **I received a B.S. in marine biology and a B.S. in chemistry.**

16:06:51 Q. **When was that?**

16:06:52 A. **I received those degrees in 1977.**

16:06:57 Q. **Did you complete any higher education?**

16:06:59 A. **I did.**

16:06:59 Q. **Did you get a Ph.D.?**

16:07:01 A. **I did. I received a Ph.D. in pharmacology.**

16:07:04 Q. **When was that?**

16:07:04 A. **1981.**

16:07:05 Q. **From where did you get the Ph.D?**

16:07:08 A. **The Medical University of South Carolina.**

16:07:12 Q. **You also have an M.D.?**

16:07:13 A. **I do.**

16:07:14 Q. **Where did you get that?**

16:07:15 A. **That was also from the Medical University of South Carolina.**

16:07:18 Q. **What years did you work on the M.D.?**

16:07:20 A. **From 1981 to 1985.**

16:07:22 Q. **Did you do any post-doctoral work?**

16:07:24 A. **I did. I completed a post-doctoral fellowship at the Medical University of South Carolina.**

16:07:30 Q. **When was that?**

16:07:32 A. **Also from 1981 to 1985.**

16:07:34 Q. **So the post-doc and M.D. were at the same time?**

16:07:37 A. **They were.**

16:07:37 Q. **Where did you go after you completed your post-doctoral work and your M.D.?**

16:07:43 A. **I became a medical staff fellow at the National Institutes of Health.**

16:07:47 Q. **What years were you there?**

16:07:49 A. **I was there from 1985 to 1987.**

16:07:53 Q. **And what did you do at the NIH?**

16:07:55 A. **I saw patients, but most of the time I worked in the**
16:07:59 **laboratory of Dr. Julius Axelrod.**
16:08:02 Q. **What were you studying or working on at NIH?**
16:08:05 A. **I was looking at the ways that receptor agonists, such**
16:08:09 **as bradykinin, activate cells.**
16:08:12 Q. **Was that the first work you did with bradykinin?**
16:08:14 A. **In graduate school I worked with Perry Halushka, so**
16:08:24 **there was a lot of bradykinin and kinin work going on there.**
16:08:29 **That's the first public -- the first published work that I**
16:08:31 **did.**
16:08:33 Q. **Could you just very briefly describe the work you did**
16:08:36 **with bradykinin at the NIH in '85 to '87?**
16:08:42 A. **I was interested in bradykinin activation of cells**
16:08:45 **leading to phospholipidase activation.**
16:08:49 Q. **Were you working on bradykinin antagonists or agonists**
16:08:52 **at the NIH?**
16:08:53 A. **I was working on the agonists at the NIH.**
16:08:59 Q. **Was that in vitro cell work?**
16:09:02 A. **Almost all of it was in vitro.**
16:09:03 Q. **Could you explain what kind of in vitro cell work you**
16:09:06 **were doing?**
16:09:06 A. **We isolated cells from a number of different tissues,**
16:09:09 **put them in the tissue culture, and then stimulated them**
16:09:13 **there.**
16:09:13 Q. **Where did you go after your fellowship at NIH?**

16:09:17 A. **I began work at Nova Pharmaceutical.**

16:09:19 Q. **When was that?**

16:09:20 A. **August of 1987.**

16:09:22 Q. **Did you work on bradykinin antagonists at Nova?**

16:09:25 A. **I did.**

16:09:26 Q. **All right. We're going to come back to that. We'll skip it for the moment because that's where we'll spend our time.**

16:09:31 **Why did you leave Nova?**

16:09:33 A. **Nova was in late merger discussions with Scios Corporation in late 1991. It seemed that the merger would take place and I would have to move to California, which wasn't in my interest, so I left at that time.**

16:09:51 Q. **Where did you go after Nova?**

16:09:52 A. **To Rhone Poulenc in Collegeville, Pennsylvania.**

16:09:55 Q. **How long were you there?**

16:09:56 A. **About a year.**

16:09:57 Q. **And what was your title?**

16:09:58 A. **My title there was Director of Inflammation and Bone Metabolism Research and General Pharmacology.**

16:10:09 Q. **We don't need to run through every job you've had in detail, but after you left Rhone Poulenc, did you continue to work in the pharmaceutical industry?**

16:10:17 A. **Yes. For the past more than 30 years I've worked in the pharmaceutical industry, a number of companies.**

16:10:22 Q. **Can you just briefly describe the types of work you've done?**

16:10:25 A. **At Zeneca, I was Director of Biosciences for the US and Global CNT Therapeutics area. Purdue Pharma, Vice President of Immunotherapy. Then I started AlgoRx Pharmaceuticals, which is a pain company, and ran that until we sold it.**

16:10:47 **Then started Cure Therapeutics, which was also involved in pain, but of a different type. Ran that until we sold it. Then I was one of the founding members of Pacira Pharmaceuticals. I was medical, chief medical officer. Developed their Bupivacaine liposome product for Phase 3.**

16:11:09 **After that I was one of the founders of Naurex Pharmaceuticals, which was interested in psychiatry and neurology, and ran the medical -- I was the chief medical officer and ran regulatory affairs there until we sold that two years ago.**

16:11:25 Q. **I think you said that you're currently CEO of Sanguistat. What does Sanguistat do?**

16:11:30 A. **Sanguistat is a medical device company that's developing devices to treat acute and chronic bleeding disorders.**

16:11:36 Q. **Now, Dr. Burch, did any of your work after Nova involve bradykinin antagonists?**

16:11:45 A. **It did not.**

16:11:46 Q. **Have you published peer-reviewed papers in the field of bradykinin antagonists?**

16:11:50 A. **I have.**

16:11:52 Q. **Are those publications listed in your C.V.?**

16:11:53 A. **They are.**

16:11:55 Q. **Did you contribute to any books about bradykinin?**

16:11:56 A. **I edited a book entitled "Bradykinin," and a couple of years later co-authored a book about the molecular pharmacology and molecular biology of bradykinin receptors.**

16:12:00 Q. **And if we go in your C.V. to PTX-230.16, entry 84, could you just explain to the Court what this book refers to here?**

16:12:04 A. **So that is the book that I edited called "Bradykinin Antagonists: Basic and Clinical Research."**

16:12:07 Q. **And if we turn then further in to PTX-230.23, entry 166 in your C.V., could you explain what this book is?**

16:12:11 A. **That is the book that I co-authored with two other workers at Nova, Thomas Stormann, who was a molecular biologist, and Donald Kyle, who was in charge of the medicinal chemistry entitled molecular biology and pharmacology of bradykinin receptors.**

16:12:20 Q. **Do you contribute to any publications on bradykinin currently?**

16:12:23 A. **I wrote the chapter on bradykinin in the Encyclopedia**

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16:13:12 **of Medical Chemistry, which has a new edition every eight or**
16:13:17 **nine years.**
16:13:17 Q. **Have you ever lectured or presented at a conference on**
16:13:19 **bradykinin antagonists?**
16:13:20 A. **I have.**
16:13:21 Q. **And during what time period did you do most of the**
16:13:24 **peer-reviewed research or publication and lectures on**
16:13:28 **bradykinin antagonists?**
16:13:29 A. **It was while I was at Nova, just after that, from the**
16:13:32 **late 1980s to the mid 1990s.**
16:13:35 Q. **All right, Dr. Burch. I want to go back to the period**
16:13:39 **of time that you were working at Nova.**
16:13:41 **I think you said you were hired in August of**
16:13:44 **1987. Had you worked with Nova before you were formally**
16:13:49 **hired by them?**
16:13:49 A. **In early 1987, I was approached by my mentor, Julius**
16:13:55 **Axelrod, at the NIH, who noted that he was on the scientific**
16:13:58 **advisory board of Nova, and that Nova had in-licensed a**
16:14:04 **group of bradykinin antagonists and was struggling to find**
16:14:08 **rapid and robust assays with which to screen those and**
16:14:13 **wondered if I would be willing to talk to them since I did**
16:14:17 **very simple, fast assays.**
16:14:19 Q. **And did you talk to the people at Nova while you were**
16:14:21 **still working at NIH?**
16:14:23 A. **I initially spoke to Larry Steranka, who was in charge**

16:14:26 **of the bradykinin antagonist program, told him what I did.**

16:14:29 Q. **And did you describe the assays to him?**

16:14:32 A. **I did.**

16:14:32 Q. **Did you meet with Dr. Steranka before you started working at Nova?**

16:14:36

16:14:37 A. **Yes. A couple of weeks later he visited my lab at the NIH and I actually demonstrated the assays for him.**

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16:14:45 Q. **How did you then get hired at Nova for a permanent position?**

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16:14:49 A. **At that time it was nearing the end of my fellowship and I was looking for new jobs. In fact, I had already accepted a residency in anatomic pathology at the NIH, and Dr. Axelrod said that Nova was expanding the bradykinin program, would I be interested in working there.**

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16:15:05 Q. **Did you say yes?**

16:15:07 A. **I did.**

16:15:07 Q. **And what projects was Nova working on when you arrived?**

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16:15:11 A. **When I arrived, their most established group of projects was in the area of central nervous system diseases. They were looking for a number of receptors.**

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16:15:22 **The second largest program was the cardiovascular program that was being funded by Marion Laboratories, and the bradykinin antagonist program was the newest program that existed for about two years at that**

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16:15:35 **point.**

16:15:35 Q. **Which of those products or projects were you hired to**

16:15:39 **work on?**

16:15:39 A. **I worked on the bradykinin program.**

16:15:42 Q. **And what was the purpose of the bradykinin project**

16:15:46 **when you arrived at Nova?**

16:15:47 A. **When I arrived at Nova, Nova had in-licensed a library**

16:15:53 **of about 300 peptide bradykinin antagonists from John**

16:15:57 **Stewart and Ray Vavrek. They were looking at them to**

16:16:01 **determine if any of them had appropriate properties to be**

16:16:04 **clinical candidates, and my job was to develop assays to**

16:16:09 **screen those more quickly.**

16:16:11 Q. **When you got to Nova, how did you learn about**

16:16:14 **bradykinin antagonists so you could join the project and do**

16:16:17 **your job?**

16:16:17 A. **I spoke to Drs. Stewart and Vavrek. I had actually**

16:16:22 **met Dr. Stewart in the past in regard to other things**

16:16:27 **than bradykinin. I also spoke to the staff who were**

16:16:30 **working on bradykinin at Nova, antagonists, and read the**

16:16:35 **literature.**

16:16:35 Q. **And what was going on in the bradykinin project at**

16:16:41 **Nova when you joined in 1987?**

16:16:43 A. **When I joined in 1987, the assays were based on smooth**

16:16:49 **muscle contraction and relaxation, which is a relatively**

16:16:53 **slow process compared to other ways to assess things.**

16:16:59 **Nova had also engaged in a couple of investigator sponsored clinical trials as proof of concept.**

16:17:03 Q. **Now, did there come a time when Nova started to synthesize its own or additional bradykinin antagonists?**

16:17:07 A. **It did. Soon after I arrived and we had a chance to look through the compounds, it became clear that none of them were bona fide clinical candidates, so at that point we began to both transfer medicinal chemists who were already at Nova to the bradykinin program and to hire additional medicinal chemists.**

16:17:14 Q. **What was Nova looking for in the new bradykinin antagonists you all were making?**

16:17:36 A. **Well, Stewart had made, you know, a great advance in developing the first antagonist. He had outlined the basic rules, but the antagonists he had on hand at that time were not very potent. Thirty to 50 nanomolar in receptor binding and fairly metabolically unstable. Bradykinin has a very short half life, 15 seconds. NPC567, which was the compound we tended to use most, had a half life of about ten minutes. Still very short.**

16:17:39 Q. **Now, I know you said I think that your role started focusing on the assays and biology at Nova. At some point did your responsibilities change at Nova? Did you get promoted?**

16:17:42 A. **In early 1988, I became group leader at that point.**

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16:18:30 **All of the pharmacologists in the program reported to me as**
16:18:33 **well as the medicinal chemists.**
16:18:37 Q. **At that point about how many people were reporting to**
16:18:40 **you on the bradykinin project?**
16:18:41 A. **At that point there were, including me, four Ph.D.**
16:18:46 **level pharmacologists, about eight technicians. There were**
16:18:50 **four Ph.D. medicinal chemists and each of them had one to**
16:18:55 **two technicians.**
16:18:56 Q. **Can you name some of the medicinal chemists you worked**
16:18:58 **with on the project?**
16:18:59 A. **At the beginning, there was Don Kyle, Barry Scherer,**
16:19:05 **John Carter and Roger Kleiner.**
16:19:08 Q. **And how about the pharmacologists who worked on the**
16:19:11 **project at Nova?**
16:19:12 A. **The most senior was Steve Farmer. There was also**
16:19:20 **James Sullivan, Lalita Noronha-Blob and Jimmy Vadder.**
16:19:26 Q. **Now, by 1988, was Nova working alone on its bradykinin**
16:19:31 **antagonist project?**
16:19:33 A. **In 1988, Nova entered into a joint development**
16:19:37 **agreement with SmithKline Beckman for bradykinin**
16:19:42 **antagonists.**
16:19:42 Q. **Was Nova, with SmithKline the only company working on**
16:19:47 **bradykinin antagonists at the time?**
16:19:48 A. **There were other companies that were doing early work.**
16:19:53 **At conferences Sanofi was probably the most visible. They**

16:19:57 **had published some abstracts on some early structures for**
16:20:01 **non-peptide antagonists. Fujisawa had a couple of**
16:20:07 **abstracts, but at meetings, Merck was often involved, many**
16:20:12 **of the other large pharmaceutical companies.**
16:20:14 Q. **Did you attend meetings or conferences on bradykinin**
16:20:16 **antagonists at the time?**
16:20:17 A. **I did. Our other members of the group attended all of**
16:20:21 **the conferences.**
16:20:22 Q. **Now, specifically in this 1988/1989 time frame while**
16:20:26 **you were at Nova, were you aware that Hoechst -- were you**
16:20:29 **personally aware that Hoechst had a bradykinin antagonist**
16:20:32 **program?**
16:20:33 A. **I was not. No.**
16:20:36 Q. **When did you first become aware of the Hoechst**
16:20:39 **program?**
16:20:39 A. **In 1991.**
16:20:40 Q. **And how did you come about that knowledge? How did**
16:20:43 **you learn about the Hoechst program?**
16:20:45 A. **At the International Bradykinin Conference that year**
16:20:49 **in Munich, Germany, Hoechst, Dr. Scholkens was there,**
16:20:54 **presented a paper that described a number of their**
16:20:57 **antagonists and their biological activity.**
16:21:00 Q. **In the binder in front of you, if you could turn to**
16:21:02 **PTX-28.**
16:21:07 A. **Yes.**

16:21:07 Q. **Have you seen this paper before?**

16:21:09 A. **I have.**

16:21:10 Q. **And when did you see it?**

16:21:12 A. **This is what's called an extended abstract from that bradykinin antagonist meeting. All of the presenters wrote slightly enhanced descriptions of the work they presented there. It was published in 1992.**

16:21:29 Q. **And if you turn then to the second page, PTX-28.2, it says on the bottom, and look at Table 1.**

16:21:36 A. **Yes.**

16:21:37 Q. **Did you see this table and data at the conference you were at in 1991?**

16:21:41 A. **I did.**

16:21:42 Q. **Now, were you at Nova working on any compounds that were disclosed in this table?**

16:21:49 A. **We had at that time synthesized a D-Tic-Tic compound which in this table is the fourth from the top. We had not synthesized what was on our list, D-Tic-Oic compound. There are two of those here on the second and third lines up. And also on our list, but we had not synthesized was D-Tic-Aoc on the bottom.**

16:22:17 Q. **And just focusing on the amino acid, when you refer to D-Tic and Tic, you're referring to amino acid?**

16:22:24 A. **I'm sorry.**

16:22:25 Q. **And D-Tic in the language of bradykinin antagonists**

16:22:29 **was in the seven position and Tic was in the eight position?**

16:22:32 A. **That's right.**

16:22:34 Q. **Now, had you worked on these compounds at Nova and**

16:22:38 **synthesized even some of them before you saw this work from**

16:22:42 **Hoechst?**

16:22:43 A. **We had.**

16:22:45 Q. **Did you become aware of any Hoechst patents around**

16:22:47 **this time, or patent applications, let me say?**

16:22:50 A. **Yes. When I saw the presentation at the meeting and**

16:22:53 **actually spoke a couple of times to Dr. Scholkens at the**

16:22:57 **meeting, I went back and reported that I had seen this and**

16:23:02 **what some of the peptides were. And at that time, we began**

16:23:07 **a search and discovered the European patent.**

16:23:11 Q. **To be clear, did you come across any U.S. patents at**

16:23:16 **the time?**

16:23:16 A. **No.**

16:23:17 Q. **And Dr. Scholkens was who?**

16:23:18 A. **He was one of the lead scientists in Hoechst**

16:23:22 **bradykinin antagonist program.**

16:23:26 Q. **And from your knowledge, Dr. Burch, did Nova have a**

16:23:30 **formal relationship or any relationship with Hoechst in 1989**

16:23:34 **or 1990 concerning bradykinin antagonists?**

16:23:37 A. **No.**

16:23:38 Q. **All right. Then I want to look in a little more**

16:23:44 **detail at some of the compounds that Nova was working on.**

16:23:47 **Will?**

16:23:47 **When you were at Nova, were any of Nova's**
16:23:53 **bradykinin antagonists undergoing clinical trial?**

16:23:56 A. **NPC 567 had undergone some.**

16:24:00 Q. **If you turn just to JTX-36.**

16:24:05 A. **Yes.**

16:24:05 Q. **Do you recognize this paper?**

16:24:07 A. **I do.**

16:24:07 Q. **What is it?**

16:24:08 A. **It's a paper that was written by Dr. Larry Steranka,**
16:24:17 **and a number of the folks at Nova and Dr. Stewart and Vavrek**
16:24:24 **were also authors. It describes the activity of several of**
16:24:28 **the early Stewart and Vavrek compounds.**

16:24:32 Q. **Now, just to be clear, you're not an author on this**
16:24:35 **paper; is that correct?**

16:24:35 A. **No. This work was done before I arrived.**

16:24:37 Q. **But were you familiar with this work while you were**
16:24:41 **working at Nova?**

16:24:42 A. **Yes.**

16:24:42 Q. **And what type of studies are described in this paper?**

16:24:51 A. **This --**

16:24:54 **MR. HAUG: Objection, Your Honor. I think**
16:24:55 **he's now asking for an expert view of this article which**
16:24:57 **he has nothing to do with and he's not an expert for this**
16:25:00 **case.**

16:25:00 **THE COURT: Mr. Wiesen?**

16:25:01 **MR. WIESEN: I'm trying to stay away from**
16:25:03 **expert testimony. I will withdraw the question and just**
16:25:05 **look at the specific data that he did work on while he was**
16:25:08 **at Nova.**

16:25:09 **THE COURT: All right?**

16:25:10 **MR. HAUG: That's fine. Thank you.**

16:25:11 **BY MR. WIESEN:**

16:25:12 Q. **Let's just skip then to JTX 36.2 and look at Table 1.**
16:25:20 **Do you see the series of compounds here?**

16:25:22 A. **Yes, I do.**

16:25:23 Q. **And were you familiar with these compounds while you**
16:25:25 **were at Nova?**

16:25:26 A. **Yes.**

16:25:27 Q. **The left-hand column says NPC number. Do you see**
16:25:31 **that?**

16:25:31 A. **I do.**

16:25:32 Q. **What does NPC stand for?**

16:25:34 A. **That stands for Nova Pharmaceutical Corporation.**

16:25:36 Q. **And what are the sequences that are beside that?**

16:25:40 A. **The sequences are of the modified bradykinin**
16:25:46 **antagonist.**

16:25:47 Q. **Do you see the first entry there, NPC 349?**

16:25:51 A. **I do.**

16:25:52 Q. **What's that?**

16:25:53 A. **That is a -- it's bradykinin that has the addition of**
16:25:58 **D-Arginine at the N-terminus and a substitution of Hyp at**
16:26:09 **the three position, D-Phe at the seven position.**
16:26:14 Q. **And was there another number that NPC 349 was known by**
16:26:19 **that Dr. Stewart had given the compound first?**
16:26:21 A. **Yes. Stewart named, had numbers for all of his**
16:26:24 **compounds to keep track of them. They all -- for this**
16:26:29 **program, they all began with the letter "B." He was working**
16:26:31 **with quite a number of different receptors. So this, NPC**
16:26:37 **349 was B3824.**
16:26:41 Q. **So Nova renamed the Stewart compounds to yet a**
16:26:46 **different number?**
16:26:46 A. **Yes. Most companies do that because the computer**
16:26:49 **system needs a standard numbering system.**
16:26:51 Q. **And then what was NPC567?**
16:26:54 A. **NPC567 was a very close analog of NPC 349 in that it**
16:27:02 **had the D-arg addition, the hydroxyproline at the three**
16:27:08 **position, but it did not have the Thi at the five and eight**
16:27:15 **position.**
16:27:15 Q. **Now, did you analyze the relative strength of these**
16:27:17 **antagonists at the time you were working at Nova?**
16:27:19 A. **Yes.**
16:27:19 Q. **And what did you conclude about the relative**
16:27:22 **antagonist potency of these analogs?**
16:27:25 A. **NPC 349 is slightly more potent than NPC567. 25 to**

16:27:32 **50 percent more potent.**

16:27:34 Q. **Then why was NPC567 put into the clinic if NPC 549 was**

16:27:41 **a little bit more potent?**

16:27:42 A. **There were two reasons. The primary reason is that**

16:27:44 **NPC 349 is a partial agonist in many bioassays which would**

16:27:51 **make its development as a drug problematic in many cases.**

16:27:55 **The second reason is that Stewart and Vavrek had**

16:27:57 **provided NPC567 to quite a few academic investigators, so a**

16:28:03 **fairly large literature had begun to develop around it, so**

16:28:06 **we used it as a standard compound.**

16:28:10 Q. **What were the indications for NPC567 you were**

16:28:13 **exploring at Nova?**

16:28:15 A. **During the time I was at Nova, the common cold was**

16:28:19 **explored. Airway hyperreactivity in asthmatic individuals,**

16:28:27 **actually acute asthma attacks, and then a number of no**

16:28:31 **successive pain condition.**

16:28:33 Q. **Did Nova's work with bradykinin antagonists end with**

16:28:37 **compounds like NPC 567 and NPC 349?**

16:28:42 A. **No. It just began with them. As I said, the potency**

16:28:46 **and metabolic stability didn't really meet our requirements**

16:28:49 **for a potential commercial company.**

16:28:52 Q. **What did you do next?**

16:28:53 A. **We began within the medicinal chemistry group to do**

16:28:58 **molecular modeling. We were interested in actual drug**

16:29:01 **design. The modeling suggested that rigidity was necessary,**

16:29:04 **so we began synthesizing antagonists based on NPC567**
16:29:10 **structure, but with very rigid, unnatural amino acid**
16:29:15 **substitutions.**
16:29:17 Q. **And in your work at Nova, were there particular**
16:29:20 **locations in the bradykinin antagonists from Stewart that**
16:29:23 **you were focused on in making these modifications?**
16:29:27 A. **In the molecular modeling studies, the suggestion for**
16:29:31 **both bradykinin and NPC567 is that the part of the molecule**
16:29:36 **that interacted with the receptor were residues 6, 7, 8 and**
16:29:41 **9. Stewart had found that residue seven was very important**
16:29:44 **for antagonist activity, so he focused on that first. And**
16:29:49 **then on residue 8, the thienylalanine, which confers good**
16:29:56 **potency compared to its other analogs. We also introduced**
16:30:00 **more rigid substitutions there.**
16:30:01 Q. **Methodologically, how did Nova go about synthesizing**
16:30:06 **these compounds?**
16:30:07 A. **We always synthesized using automated peptide**
16:30:10 **synthesis.**
16:30:12 Q. **Generally speaking, about how long did it take to make**
16:30:14 **a peptide?**
16:30:15 A. **Each machine could make four of them in less than a**
16:30:19 **day.**
16:30:20 Q. **How many bradykinin antagonist peptides were made at**
16:30:23 **Nova during your time?**
16:30:25 A. **Oh, several hundred.**

16:30:26 Q. **Were you trying to improve certain properties?**

16:30:29 A. **We were trying to improve potency as antagonists, so receptor binding and then in vitro antagonist activity, and we were trying to improve metabolic stability.**

16:30:43 Q. **Did you also test the compounds for activity?**

16:30:45 A. **We did.**

16:30:46 Q. **What type of tests did you use?**

16:30:48 A. **Initially, we would use bradykinin binding assays to determine whether the compounds bound to the receptors. Those that bound with reasonable potency we subjected to in vitro tests, usually with smooth muscle preparations to determine whether they were agonists or antagonists.**

16:31:07 Q. **About how long did it take at Nova to generate in vitro activity data?**

16:31:12 A. **Usually, three or four days following receipt of the compound by the pharmacologist. They had done the receptor binding on the in vitro activity.**

16:31:24 Q. **And did you also do in vivo testing?**

16:31:26 A. **We did.**

16:31:27 Q. **About how long did it take to do that?**

16:31:29 A. **That was done after the in vitro testing, and each of the in vivo models took less than a day.**

16:31:37 Q. **So how long was it's for Nova after synthesizing a compound that you have in vitro and in vivo data on the activity?**

16:31:43 A. **Usually within the week that they were synthesized.**

16:31:48 Q. **All right. We've talked a little bit about the general approach you took. I want to talk about one particular bradykinin antagonist Nova made and published.**

16:31:56 **Can you turn to JTX-9 in your binder.**

16:32:01 A. **Yes.**

16:32:02 Q. **Have you seen this paper before?**

16:32:03 A. **I have.**

16:32:04 Q. **What is it?**

16:32:05 A. **It's a paper in the "Journal of Medicinal Chemistry" that describes the initial molecular modeling work that we did and then several compounds that were synthesized to test the hypothesis generated by the model.**

16:32:34 Q. **When was it published?**

16:32:40 A. **1991.**

16:32:42 Q. **Is this paper representative of the kind of work you were doing at Nova in the late eighties and early nineties?**

16:32:50 A. **It is.**

16:32:52 Q. **If you turn to JTX-9.3 and look at Figure 1 in the upper left-hand corner?**

16:32:59 A. **Yes.**

16:33:00 Q. **What is shown here?**

16:33:01 A. **These are the structures of five model peptides. They were among the earliest peptides that we made.**

16:33:11 Q. **Did Nova come up with the structure of these peptides**

16:33:16 **and synthesize them on their own?**

16:33:19 A. **Yes.**

16:33:19 Q. **Can you describe how you went about doing that?**

16:33:22 A. **Again, this first solid phase automated synthesis, the**

16:33:28 **residues were given to us based on molecular modeling, so**

16:33:31 **these are the results in Figure 3.**

16:33:31 Q. **When you say residues, you mean the particular amino**

16:33:34 **acids?**

16:33:34 A. **Yes.**

16:33:40 Q. **If we look at just peptides 1 through 4, what did you**

16:33:46 **put in the 7 position of the bradykinin antagonists?**

16:33:50 A. **Peptides 1 through 4 all had D-Tic.**

16:33:52 Q. **What is D-Tic?**

16:33:54 A. **D-Tic is phenylalanine with an extra methylene group**

16:34:00 **that ties the ring back to the peptide backbone, which makes**

16:34:06 **the compound unable to rotate around the axis. It confers a**

16:34:12 **great deal of rigidity.**

16:34:15 Q. **You mentioned you used the D-Tic. Why the D-Tic?**

16:34:19 A. **We actually synthesized the L and D, all of the active**

compounds of D-Tic, which is synthesis with these

16:34:28 **phenylalanines.**

16:34:28 Q. **We talked about the 7 position that Nova was working**

16:34:32 **with. On these peptides what did you all put in the 8**

16:34:36 **position of the bradykinins?**

16:34:40 A. **Initially we put L-Tic, because that was a more rigid**

16:34:44 **analog of the residues that were in that position. We also**
16:34:50 **tried D-Tic. D-Tic had very poor activity there. Then we**
16:34:55 **tried Aoc, which was another rigid analog smaller than Tic**
16:35:00 **and was more consistent with the proline that would be in**
16:35:05 **bradykinin.**
16:35:05 Q. **Dr. Burch, when did you at Nova first synthesize a**
16:35:10 **bradykinin antagonist with D-Tic in the 7 position?**
16:35:15 A. **Early 1989.**
16:35:17 Q. **Going back now to JTX-9.3, I want to look at a**
16:35:22 **different part of that page of the paper, if we can go down**
16:35:25 **to the bottom right-hand corner, the text there, you see --**
16:35:29 **the text above. You see the sentence there that says,**
16:35:34 **Although peptides 1 and 3 have been recently disclosed in a**
16:35:39 **European patent application describing them as bradykinin**
16:35:43 **antagonists, did you write that?**
16:35:45 A. **Yes.**
16:35:45 Q. **What were peptides 1 and 3 that you are referring to**
16:35:49 **there?**
16:35:49 A. **Peptide 1 was the D-Tic 7 Aoc 8, and peptide 3 was**
16:35:57 **what D-Tic 7 AOC.**
16:36:01 Q. **You see that sentence with Footnote 17 that cites to a**
16:36:06 **European patent application, to Henke, et al. Do you see**
16:36:09 **that?**
16:36:09 A. **Yes.**
16:36:10 Q. **How did you come to discover that European patent**

16:36:13 application that is cited here in JTX-9, Footnote 17?
16:36:17 A. This patent was discovered as a result of my coming
16:36:21 back from from the '91 meeting disclosing these peptides.
16:36:31 Q. Who was this European application owned by?
16:36:36 A. Hoechst.
16:36:36 Q. Had you identified and developed these compounds
16:36:38 before you saw this Hoechst European patent application?
16:36:42 A. Of those two particular peptides, 1 and 3, that were
16:36:44 in the patent application, we had already synthesized and
16:36:49 tested D-Tic. By the time we found about this Aoc compound,
16:36:56 D-Tic had been on our list but had not been synthesized by
16:37:01 Nova.
16:37:01 Q. If we turn to JTX-9.5, the last page, underneath the
16:37:08 authors' names there, you see the date this was submitted?
16:37:11 A. Yes.
16:37:11 Q. When was it submitted?
16:37:13 A. December 10, 1990.
16:37:15 Q. Does that mean you knew about the Hoechst European
16:37:19 patent by December 10, 1990?
16:37:22 A. No. This original manuscript was submitted in early
16:37:25 1990 -- excuse me, it was December 10, 1990, but the
16:37:34 manuscript had a number of reviewers' comments that needed
16:37:38 to be addressed, which takes a while. During that time we
16:37:44 attended the meeting and discovered the patent.
16:37:46 Q. You added the patent citation in later?

16:37:49 A. **We did.**

16:37:49 Q. **If we go back then to the text and we put up JTX-9.3 and carrying over to JTX-9.4, after the footnote then, you all wrote, "The former was discovered coincidentally and independently in our laboratories."**

16:38:34 **Can you just explain what you meant by that?**

16:38:36 A. **That means that we had synthesized it and evaluated it coincidentally with Hoechst in the sense that we didn't know that they had done that work.**

16:38:48 Q. **Did this peptide, this D-Tic-Tic peptide we have been talking about, did it have an NPC name or number?**

16:38:56 A. **Yes, it was called NPC 16731.**

16:39:01 Q. **Do you remember about when you first synthesized that peptide?**

16:39:05 A. **That would have been synthesized either late '89 or early 1990.**

16:39:11 Q. **Dr. Burch, was NPC 16731 the only compound Nova made or considered making with D-Tic in the 7 position, I should clarify, other than the compounds we have seen?**

16:39:21 A. **No. Over a couple of years we made dozens of them.**

16:39:24 Q. **What other amino acids did Nova consider putting in the 8 position in the bradykinin antagonists it created with D-Tic in the 7 position?**

16:39:31 A. **We looked at other residues that were both aliphatic and aromatic but small. And we considered mostly rigid**

16:39:43

16:39:49 **structures, one that proved quite successful was Oic.**

16:39:56 Q. **Did you actually at Nova make a compound with D-Tic in**

16:40:00 **the 7 position and Oic in the 8 position?**

16:40:05 A. **Yes.**

16:40:06 Q. **When did you do that approximately?**

16:40:08 A. **Sometime in the 1990 range.**

16:40:09 Q. **You said the 1990 range?**

16:40:12 A. **Yes.**

16:40:12 Q. **That compound we were discussing, NPC 16731 but with**

16:40:17 **Oic at the 8 position, does that compound have a different**

16:40:21 **name today?**

16:40:22 A. **Its formal generic name is icatibant, yes.**

16:40:27 Q. **To be clear, when you considered making and made that**

16:40:30 **compound, had you seen that compound published by Hoechst?**

16:40:33 A. **No. We had it at our office.**

16:40:35 Q. **I also want to be clear, Dr. Burch, are you saying you**

16:40:39 **made it before Hoechst made it?**

16:40:41 A. **No.**

16:40:41 Q. **I want to look at the activity of the NPC 16731**

16:40:51 **compared to that prior compound NPC 567. Can you turn to**

16:40:56 **JTX-41 in your binder?**

16:40:59 A. **Yes.**

16:41:00 Q. **Do you recognize this paper?**

16:41:01 A. **I do.**

16:41:02 Q. **What is it?**

16:41:03 A. **It was a paper that was published by our group at Nova**
16:41:07 **with Steve Farmer as the first author that described the**
16:41:15 **biological activity of the D-Tic-7-D-Tic-8 compound**
16:41:19 **NPC 16731.**
16:41:21 Q. **The R.M. Burch author, is that you?**
16:41:24 A. **Yes.**
16:41:25 Q. **When was this published?**
16:41:27 A. **1991.**
16:41:28 Q. **What do you describe in this publication?**
16:41:32 A. **At this time while we were doing this work, the**
16:41:34 **Stewart and Vavrek compounds were showing good activity as**
16:41:37 **antagonists in some positions, but for the most part they**
16:41:40 **were mostly inactive in pulmonary tissues, which is one of**
16:41:44 **the sites we were interested in. NPC 16731 had very good**
16:41:49 **activity in the pulmonary smooth muscle contraction. So we**
16:41:52 **published our results of that.**
16:41:56 Q. **If we turn to JTX-41.2, the Discussion section on the**
16:42:03 **right-hand column, pull that out.**
16:42:07 **What results did you get for the activity of NPC**
16:42:10 **16731 compared to NPC 567?**
16:42:16 A. **NPC 567, as I mentioned, was a very poor in the**
16:42:21 **pulmonary system. We found that NPC 16731 was more than a**
16:42:27 **hundredfold more potent in binding, and about fifty-fold**
16:42:32 **greater potency in the smooth muscle contraction assays.**
16:42:36 Q. **How did you interpret that data at Nova at that time?**

16:42:40 A. **We thought it was very good confirmation of the**
16:42:47 **hypothesis that we had made that adding rigidity would**
16:42:51 **increase potency.**
16:42:51 Q. **Now, at the time, was it your view at Nova that this**
16:42:57 **was potent enough to actually be used as a drug?**
16:43:00 A. **Certainly, the potency was consistent with being used**
16:43:03 **as a drug. At that time we didn't consider putting it into**
16:43:06 **the clinic in that it was the first compound in the series,**
16:43:08 **and we wanted to explore the structure/ activity to see, A,**
16:43:11 **if we could increase the potency more, and B, increase**
16:43:18 **metabolic affinity more.**
16:43:18 Q. **Is the testing and work described in JTX-41 that we**
16:43:22 **have been looking at indicative of the type of work that**
16:43:25 **Nova was doing on bradykinin antagonists in 1990 and 1991?**
16:43:30 A. **Yes, it is.**
16:43:31 Q. **In 1990 and '91 was Nova still using NPC 16731 as part**
16:43:37 **of its work on its bradykinin program?**
16:43:40 A. **We were. At that point we had actually switched our**
16:43:43 **standard compound, if you will, from NPC 567 to NPC 16731.**
16:43:49 Q. **Did Nova continue making more compounds with D-Tic in**
16:43:53 **the 7 position?**
16:43:54 A. **We did.**
16:43:59 Q. **I know you said you left Nova in the fall of 1991?**
16:44:03 A. **Yes.**
16:44:03 Q. **Was Nova still working on the bradykinin antagonist**

16:44:07 **program at that time?**

16:44:07 A. **Yes.**

16:44:07 Q. **At that time and following, was the bradykinin antagonist project still an important project at Nova?**

16:44:13

16:44:15 A. **It was.**

16:44:15 Q. **Was it the primary project at Nova anymore?**

16:44:20 A. **It was not.**

16:44:21 Q. **Why not? What happened?**

16:44:23 A. **By that time another project we had been working on, which was called the leumedins project, in which we had discovered a group of leukocyte inhibitors, had a lot of very promising data to suggest that we would have small orally active molecules to treat a number of inflammatory conditions, so we had ramped up the staffing in that project.**

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16:44:47 Q. **In fact, Dr. Burch, is it the case that at some point you suggested that Nova shut down the bradykinin antagonist project?**

16:44:50

16:44:56

16:44:56 A. **That's correct.**

16:44:56 Q. **Why was that?**

16:44:57 A. **In 1991 Nova, which was a public company, had really run out of the ability to do additional follow-on financing. That left us with a relatively small amount of cash.**

16:45:01

16:45:22

16:45:25 **I think at the time I made the suggestion we had about six weeks of cash left, which for small companies is**

16:45:29

16:45:33 not much but not a lot less than usual. And that decision,
16:45:40 our suggestion was made to enable us to put money into the
16:45:45 project that investors were willing to invest in.
16:45:49 Q. Did your bosses, the higher-ups at Nova, follow your
16:45:55 suggestion?
16:45:55 A. They did not.
16:45:55 Q. Did Nova keep working on bradykinin antagonists then?
16:45:59 A. Yes.
16:46:00 Q. Did you recently remember that after you left Nova you
16:46:03 actually did have some further communications with people
16:46:06 from Nova about later work?
16:46:08 A. Yes.
16:46:08 Q. And we looked at your C.V., that entry 166. Was that
16:46:14 a book you wrote in 1993?
16:46:16 A. That's correct.
16:46:16 Q. Can you just describe what that project was in 1993?
16:46:22 A. The 1993 book, I had been asked by the publisher,
16:46:26 which published rapid turn-around current topics of
16:46:30 interest, to write a book about the molecular biology and
16:46:36 pharmacology of bradykinin receptors and I had been involved
16:46:39 with the cloning and doing some mutagenicity studies of
16:46:44 bradykinin receptors. That book was written in 1993. As my
16:46:48 co-authors, I asked Tom Storemann, who was the molecular
16:46:54 biologist at Nova, and Don Kyle, who was the molecular
16:46:58 modeler, chief medicinal chemist, to write that with me.

16:47:04 **That book was actually written in 1993 and submitted in**
16:47:10 **mid-1993.**
16:47:11 Q. **Just to summarize your work, then, at Nova, on**
16:47:16 **bradykinin antagonists, during your time at Nova do you know**
16:47:19 **about how much money Nova was investing per month on average**
16:47:23 **on the bradykinin project?**
16:47:25 A. **At the peak we were investing about 2 million dollars**
16:47:28 **a month.**
16:47:29 Q. **During your time at Nova, about how many people were**
16:47:33 **working on the bradykinin antagonist project?**
16:47:36 A. **At the peak there were about 18 pharmacologists and 14**
16:47:39 **chemists.**
16:47:39 Q. **When you left in the fall of 1991, was Nova still**
16:47:42 **working on the bradykinin antagonist with D-Tic in the 7**
16:47:47 **position?**
16:47:48 A. **We were.**
16:47:48 Q. **When you left in the fall of 1991, about how many**
16:47:51 **people were working at least part time on the bradykinin**
16:47:55 **antagonist project?**
16:47:58 A. **They were about 14 pharmacologists and ten chemists.**
16:48:02 Q. **About how much was being spent on average in the fall**
16:48:06 **of 1991 when you left on the bradykinin antagonist project?**
16:48:11 A. **Close to a million dollars.**
16:48:14 Q. **Can you estimate about how much money Nova invested in**
16:48:17 **its bradykinin antagonist project during the time while you**

16:48:20 **were there?**

16:48:23 **MR. HAUG: Objection, Your Honor.**

16:48:24 **THE COURT: Sustained.**

MR. WIESEN: No further questions, Your Honor.

16:48:26 **All right. You may start cross-examination.**

16:48:43 **MR. HAUG: Thank you, Your Honor. May I hand out the binders?**

16:48:47 **THE COURT: Yes.**

16:49:16 **CROSS-EXAMINATION**

BY MR. HAUG:

16:49:26 Q. **Good afternoon, Dr. Burch. My name is Ed Haug. I am also representing Sanofi and Shire in this case. I want to ask you some questions.**

16:49:39 **Dr. Burch, you just testified that you left Nova in 1991. Is that right?**

16:49:43 A. **Yes.**

16:49:45 Q. **Do you recall exactly when you left?**

16:49:45 A. **I don't.**

16:49:48 Q. **Was it the fall of '91?**

16:49:49 A. **Yes.**

16:49:51 Q. **Once you terminated your employment with Nova, did you ever again have a professional relationship with Nova?**

16:49:51 A. **No.**

16:49:56 Q. **Once your employment with Nova terminated, did you ever have access to Nova confidential information?**

16:49:58

16:50:03

16:50:06 A. **I did not.**

16:50:07 Q. **Dr. Burch, once you left your employment with Nova in 1991, did you ever have information as to Nova's strategies regarding their research and development of bradykinin antagonists?**

16:50:23 A. **No.**

16:50:24 Q. **So you have no personal knowledge regarding Nova's bradykinin antagonist program after you left Nova in the Fall of 1991. Isn't that correct?**

16:50:37 A. **Just some molecules that were synthesized and some modeling that had been done through to about the middle of 1993.**

16:50:45 Q. **You have personal knowledge of that?**

16:50:48 A. **They are in the book.**

16:51:03 Q. **Dr. Burch, I would like you to turn to -- let me go back to your testimony about NPC 16731. Do you recall that?**

16:51:24 A. **Yes.**

16:51:24 Q. **NPC is Nova Pharmaceutical Corporation. Right?**

16:51:29 A. **Right.**

16:51:29 Q. **That was their designation of the compound they had synthesized. Right?**

16:51:35 A. **That's right.**

16:51:35 Q. **Were you employed at Nova at the time they synthesized the compound?**

16:51:39 A. **Yes.**

16:51:39 Q. **And, Dr. Burch, isn't it true that you, yourself, did**
16:51:44 **not design the sequence of that compound?**
16:51:46 A. **That was done prior to the development of the**
16:51:54 **synthesis.**
16:51:54 Q. **Did you have anything to do with the synthesis?**
16:51:58 A. **No.**
16:51:58 Q. **Please turn to Tab JTX-9. It should be in the binder**
16:52:05 **in front of you.**
16:52:06 **There is an article there, this is the article**
16:52:09 **you just testified about. Right?**
16:52:12 A. **Yes.**
16:52:12 Q. **You are an author on this article?**
16:52:18 A. **That is correct.**
16:52:18 Q. **If you would please turn to JTX-9.5. This is where we**
16:52:26 **see the publication date of December 10, 1990. Is that**
16:52:30 **correct?**
16:52:31 A. **Submission date.**
16:52:31 Q. **Thank you. Please turn to 9.3. I would like you to**
16:52:45 **look at Figure 1, which is in the upper left-hand corner.**
16:52:59 **Peptide No. 1, at the top, do you know what the**
16:53:04 **code name is for that?**
16:53:06 A. **That's NPC 16731.**
16:53:10 Q. **That is the 16731 compound that you were talking**
16:53:13 **about. Right?**
16:53:14 A. **Yes.**

16:53:14 Q. **And, Dr. Burch, please read aloud the sentence at the**
16:53:19 **bottom right-hand side of page JTX-9.3.**
16:53:24 **I will read it for you. It's late in the day.**
16:53:27 **Sorry. I am reading on 9.3. It says, "Although peptides 1**
16:53:38 **and 3 have been recently disclosed in a European patent**
16:53:43 **application describing them as bradykinin antagonists, the**
16:53:48 **former was discovered coincidentally and independently in**
16:53:53 **our laboratories."**
16:53:54 **Now, did I read that correctly?**
16:53:56 A. **Yes.**
16:53:56 Q. **You just testified that that is your understanding.**
16:54:00 **Is that right?**
16:54:01 A. **That's correct.**
16:54:01 Q. **You didn't write this, did you?**
16:54:03 A. **The paper, I was one of the co-authors.**
16:54:05 Q. **Did you write this sentence, that it was discovered**
16:54:09 **coincidentally and independently in our laboratories?**
16:54:11 A. **I don't recall who wrote that. My guess is it would**
16:54:15 **be Don Kyle who wrote that.**
16:54:17 Q. **But it wasn't you, was it?**
16:54:20 A. **Probably not.**
16:54:21 Q. **And peptides 1 and 3 in this sentence, they are**
16:54:27 **referring to peptides 1 and 3 at the top of the page on**
16:54:31 **JTX-9.3. Right?**
16:54:34 A. **Yes.**

16:54:34 Q. **The sentence we just read, or I just read, that peptides 1 and 3 had been disclosed in the European patent application, that is the Hoechst patent application. Right?**

16:54:46 A. **Yes.**

16:54:47 Q. **Have you looked at that patent application?**

16:54:48 A. **I did at the time, yes.**

16:54:51 Q. **And do you know if that application was also published?**

16:54:55 A. **At that time it was our impression that it was not.**

16:55:01 Q. **I would like you to look at PTX-356, which should also be in your binder. Do you have that?**

16:55:16 A. **I do.**

16:55:17 Q. **Looking at the first page of PTX-356, it is European Patent Application 89121498.3. If you look at Position 2 in the upper left-hand corner, it says Date of Receipt, can you see the date there?**

16:55:39 A. **Yes.**

16:55:39 Q. **Would you agree with me it's November 21, 1989?**

16:55:43 A. **I do.**

16:55:46 Q. **Dr. Burch, isn't it true that Nova was aware and had access to this European patent application before they submitted JTX-9 for publication?**

16:55:55 A. **No, we weren't aware of the patent application.**

16:55:58 Q. **Do you know if Don Kyle was?**

16:56:01 A. **He was not.**

16:56:03 Q. **Please turn to 356.38. Do you see where it says, 48**
16:56:13 **colon: Do you see next to the colon, do you recognize the**
16:56:28 **structure that is below that?**
16:56:30 A. **That is the molecule that we called NPC 16731.**
16:56:35 Q. **I don't know if you understand German, but it says**
16:56:39 **Beispiel. Do you know what that stands for?**
16:56:45 A. **Because of its position, I assume it means example.**
16:56:48 Q. **Isn't it correct that NPC 16731 is disclosed in the**
16:56:55 **Hoechst patent application in Example 48?**
16:56:58 A. **Yes.**
16:57:05 Q. **Now, isn't it also true that Nova had access to the**
16:57:09 **sequence of NPC 16731 as disclosed in the Hoechst patent**
16:57:16 **application -- withdrawn.**
16:57:20 **I would like you to turn to 356.34. Do you see**
16:57:30 **that structure below where it says 24 colon?**
16:57:36 **MR. WIESEN: Your Honor, I have an objection to**
16:57:38 **the continued use of this exhibit if we are going to keep**
16:57:41 **using a document in German for which no translation has been**
16:57:47 **provided.**
16:57:48 **MR. HAUG: I am only asking about the structure.**
16:57:52 **MR. WIESEN: That is fine. This page has some**
16:57:54 **text.**
16:57:55 **MR. HAUG: I am staying away from anything**
16:57:57 **German.**
16:57:58 **THE COURT: I will keep your objection in mind.**

16:58:01 **BY MR. HAUG:**

16:58:02 Q. **You do see this. Correct?**

16:58:04 A. **Yes, I see the structure.**

16:58:08 Q. **Do you recognize the structure?**

16:58:09 A. **This is the structure of peptide 3.**

16:58:14 Q. **From your article?**

16:58:18 A. **Correct.**

16:58:30 Q. **Now, Dr. Burch, please turn to PTX-357, which is also in your binder. There is also a 357T in your binder, which is an English translation of at least the cover page. So referring to PTX-357T, what is the publication date of this application, if you can tell?**

16:58:51 A. **I cannot tell. It looks like the translation was 2018. But I don't know the publication date of the patent.**

16:59:14 Q. **Can I ask you to look at the left-hand side where it says "publication date" next to [43]?**

16:59:23 A. **I am sorry. That's a translator's page.**

16:59:27 **This is 357 or 357T?**

16:59:33 Q. **357T is the English translation of the first page of PTX-357.**

16:59:42 A. **Publication date is May 30, 1990.**

16:59:45 Q. **This publication, also, if you could look at the application number right above that, do you see that, where it says Application No. 89121498.3?**

16:59:58 A. **Yes.**

16:59:58 Q. **That is the same application number as what we saw on**
17:00:03 **PTX-356, which was the Hoechst European patent application**
17:00:07 **that you referenced in your article. Isn't that correct?**
17:00:11 A. **Correct.**
17:00:11 Q. **NPC 16731, did that ever get to be a product?**
17:00:24 A. **No.**
17:00:25 Q. **Did it have the potency of icatibant?**
17:00:30 A. **It was similar.**
17:00:30 Q. **How similar?**
17:00:31 A. **I would have to go back and look at our papers. It**
17:00:36 **was a potent compound, certainly.**
17:00:41 Q. **I would like you to now look at JTX-41. I believe you**
17:01:02 **also testified about this article?**
17:01:03 A. **I did.**
17:01:04 Q. **This article, this article was published in, was it**
17:01:12 **1991?**
17:01:13 A. **1991, yes.**
17:01:14 Q. **Are you the author of this publication?**
17:01:19 A. **I am one of the authors, yes.**
17:01:21 Q. **Is the compound identified in the title 16731?**
17:01:25 A. **Yes.**
17:01:26 Q. **Could you please turn to the last page of the article**
17:01:29 **on JTX-41.3 and tell me when the article was received for**
17:01:36 **publication?**
17:01:37 A. **November 26, 1990 -- received, October 26, 1990.**

17:01:58 Q. **Now, you recommended that Nova discontinue the**
17:02:05 **bradykinin program, didn't you?**
17:02:07 A. **That's correct.**
17:02:08 Q. **And, Dr. Burch, if you would turn again to JTX-9,**
17:02:22 **which is the article we have been looking at. You have**
17:02:28 **confirmed that this discloses NPC 16731. Was this compound**
17:02:36 **ever used as a clinical lead?**
17:02:40 A. **It was not.**
17:02:42 Q. **And by the time you were leaving Nova in 1991, were**
17:02:46 **there other clinical studies ongoing on other bradykinin**
17:02:51 **antagonists by Nova?**
17:02:52 A. **Not at that time.**
17:02:54 Q. **And despite that NPC 16731 was more potent and had a**
17:03:01 **longer half-life, as you testified, than the peptide**
17:03:06 **bradykinin antagonist NPC 567 that Nova had evaluated in its**
17:03:11 **human clinical trials, Nova still did not consider NPC 16731**
17:03:19 **to be a clinical lead. Is that correct?**
17:03:22 A. **That's correct.**
17:03:23 Q. **Dr. Burch, is it true that during your time at Nova,**
17:03:28 **finances were always tight?**
17:03:30 A. **Yes.**
17:03:30 Q. **You testified about how much money was being spent per**
17:03:34 **month. I think you estimated 2 million at one point. Is**
17:03:38 **that right?**
17:03:38 A. **At the peak, yes.**

17:03:39 Q. **Do you know if any documents have been produced in this case that show the investment by Nova?**

17:03:45 A. **No, I don't. I am not aware of that.**

17:03:50 Q. **Do you recall being subpoenaed in this case?**

17:03:53 A. **Yes.**

17:03:53 Q. **And you were asked for documents?**

17:03:55 A. **Yes.**

17:03:55 Q. **And you didn't produce any documents. Correct?**

17:03:56 A. **Correct.**

17:03:57 Q. **Have you seen any documents in preparation for your testimony that would show you that they were spending 2 million dollars a month?**

17:04:03 A. **I have not seen any, no.**

17:04:06 Q. **So that is your testimony just here today going back to 1991, your best guess?**

17:04:14 A. **Yes.**

17:04:20 Q. **Now, at the time you were still --**

17:04:25 **THE COURT: Mr. Haug, if you don't have much more --**

17:04:27

17:04:30 **MR. HAUG: I have a little more. Probably 20 to 30 minutes.**

17:04:32

17:04:32 **THE COURT: I am about fried. Okay. We will resume tomorrow.**

17:04:36

17:04:38 **(Court recessed.)**